NEOPLASIA

Dr. PRIYANKA SACHDEV, MD

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DEFINITION

- The term ‘neoplasia’ means **new growth**
- The new growth produced is called ‘**neoplasm**’ or ‘**tumour**`
- The branch of science dealing with the study of neoplasms is called **oncology**

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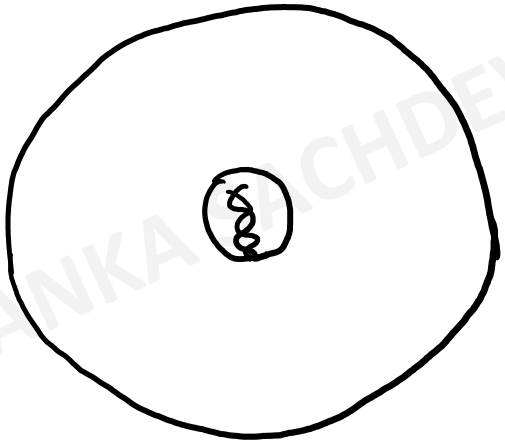
Normal Cell



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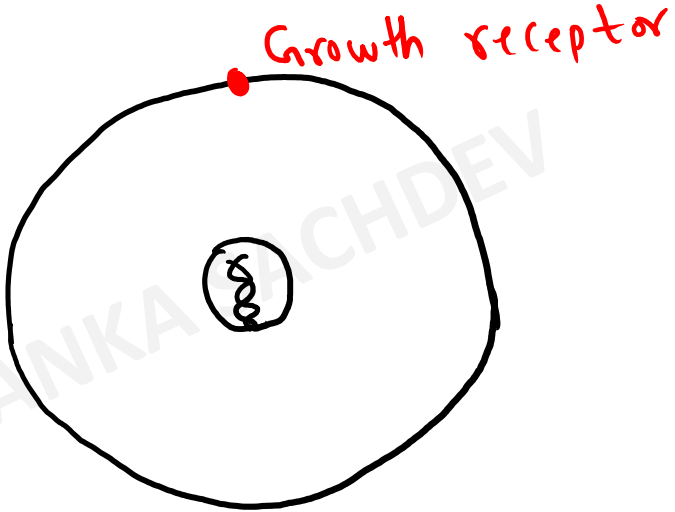
Normal Cell



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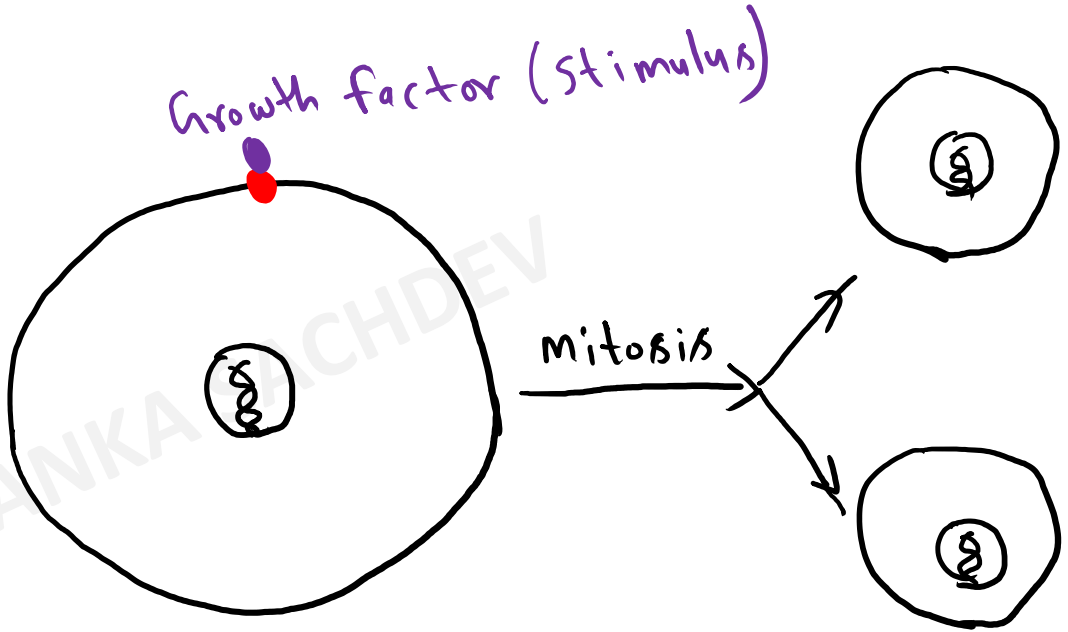
Normal Cell



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- **“A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner even after cessation of the stimuli which evoked the change.”**

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Neoplasm

An abnormal mass of tissue

- The growth of which **exceeds and is uncoordinated** with that of the normal tissues
- Persists in the same excessive manner **even after cessation of the stimuli** which evoked the change.

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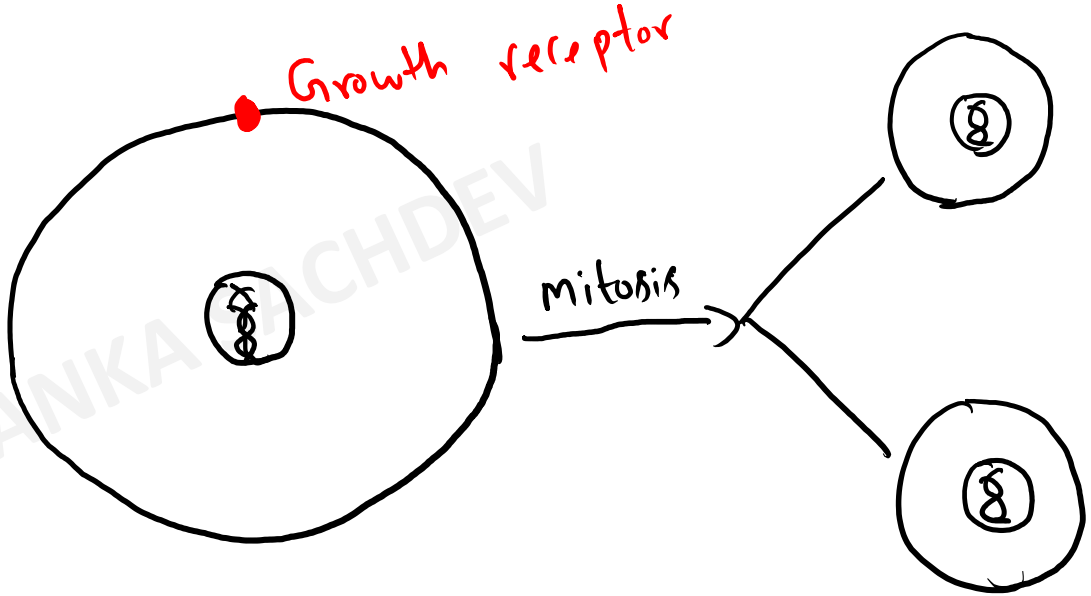
Neoplastic Cell

Absence of Growth factor (Stimulus)



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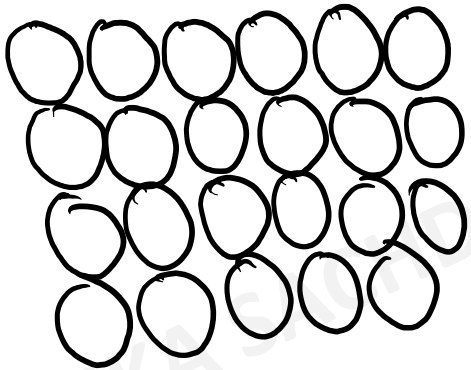

Neoplasm

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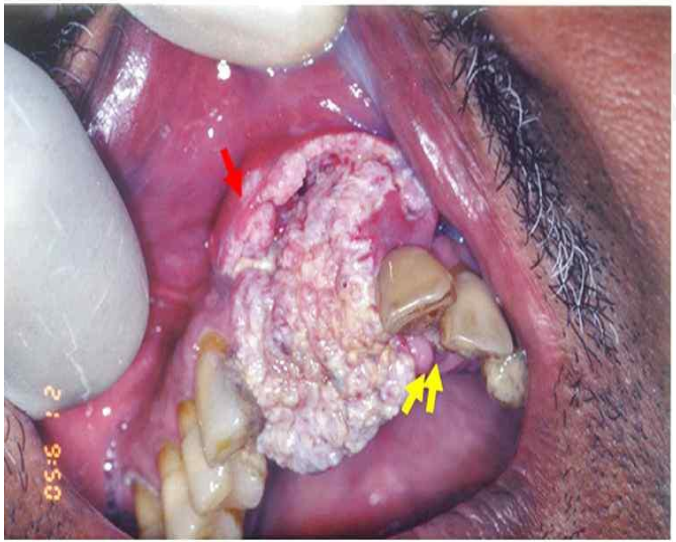

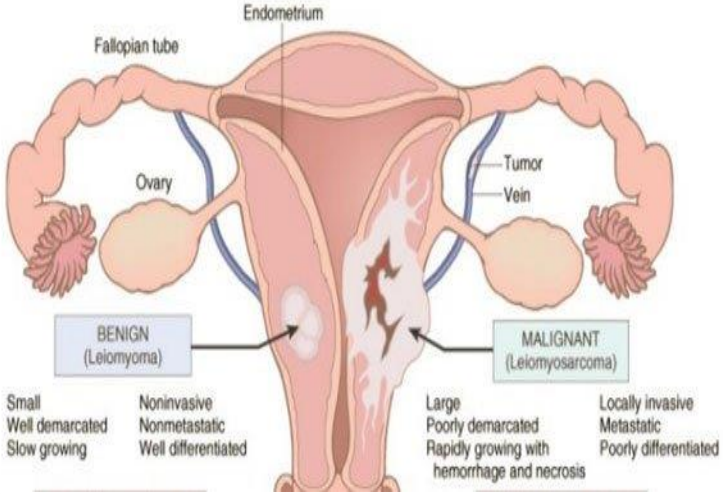

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- Neoplastic cells lose control and regulation of replication and form an abnormal mass of tissue.

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COMPONENTS

1. **‘Parenchyma’** comprised by proliferating **tumour cells**

- Parenchyma determines the nature and evolution of the tumour.

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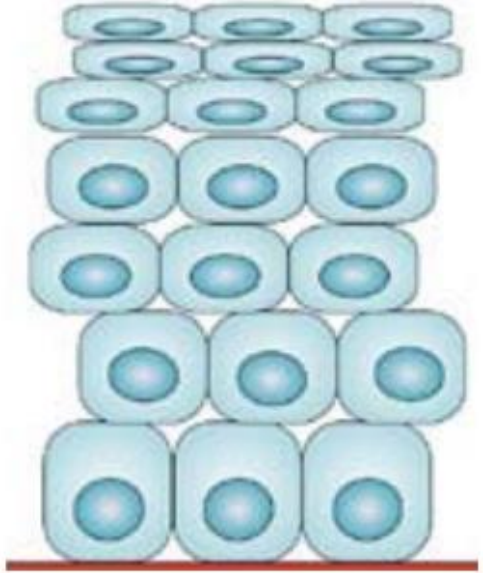
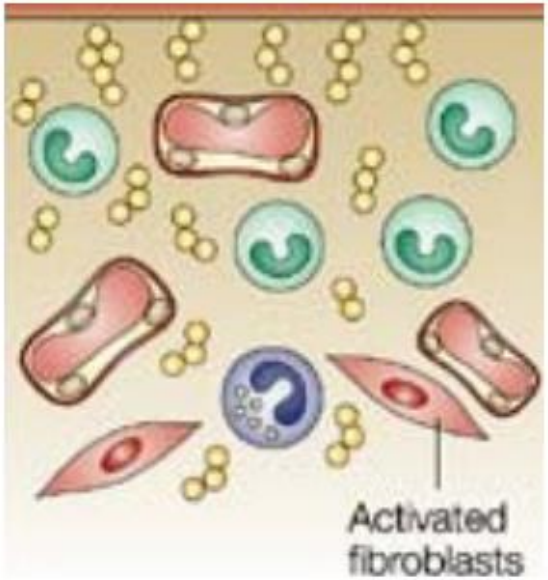
2. **‘Supportive stroma’** composed of **fibrous connective tissue and blood vessels**

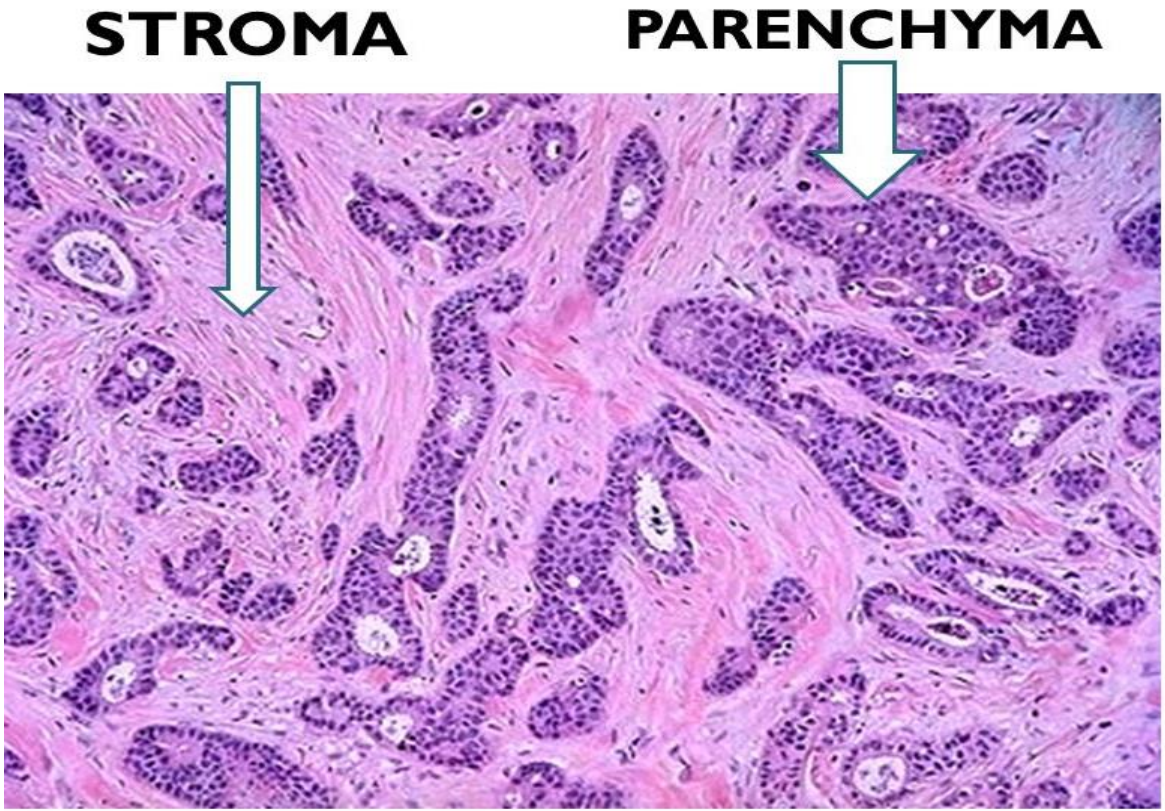
- It provides the framework on which the parenchymal tumour cells grow.

1. Proliferative neoplastic parenchyma



2. Supportive fibrovascular stroma





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- **Desmoplasia** is a term used for production of **abundant collagenous stroma by the parenchymal cells**

- It leads to **excessive fibrosis** in tumor due to formation of an abundant collagenous stroma
- e.g. in **scirrhous carcinoma of breast**

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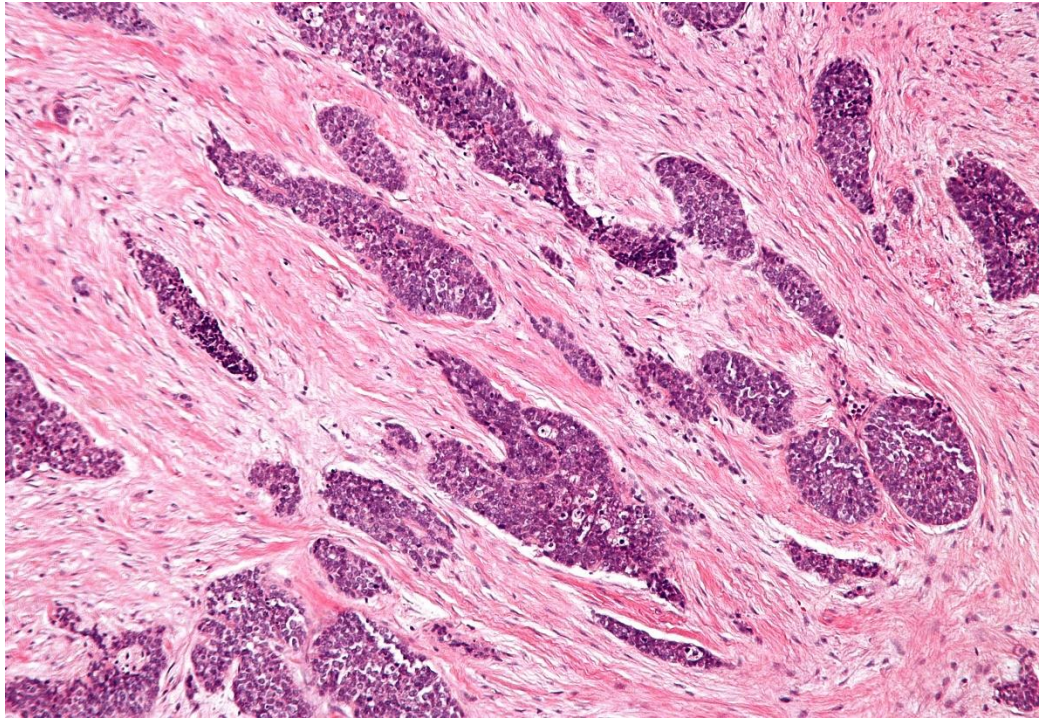

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NOMENCLATURE

A)Benign tumors

B)Malignant tumors

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Benign tumors

- Benign tumors are designed by attaching the suffix – **“oma”**

e.g

1. Tumor of fibroblasts (fibroma)
2. Tumor of cartilagenous cells (chondroma)
3. Tumor of osteoblasts (osteoma)

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- **Adenoma** - Benign epithelial tumor arising from glands or forming a glandular pattern
- **Papilloma** - Benign tumor with finger-like projections

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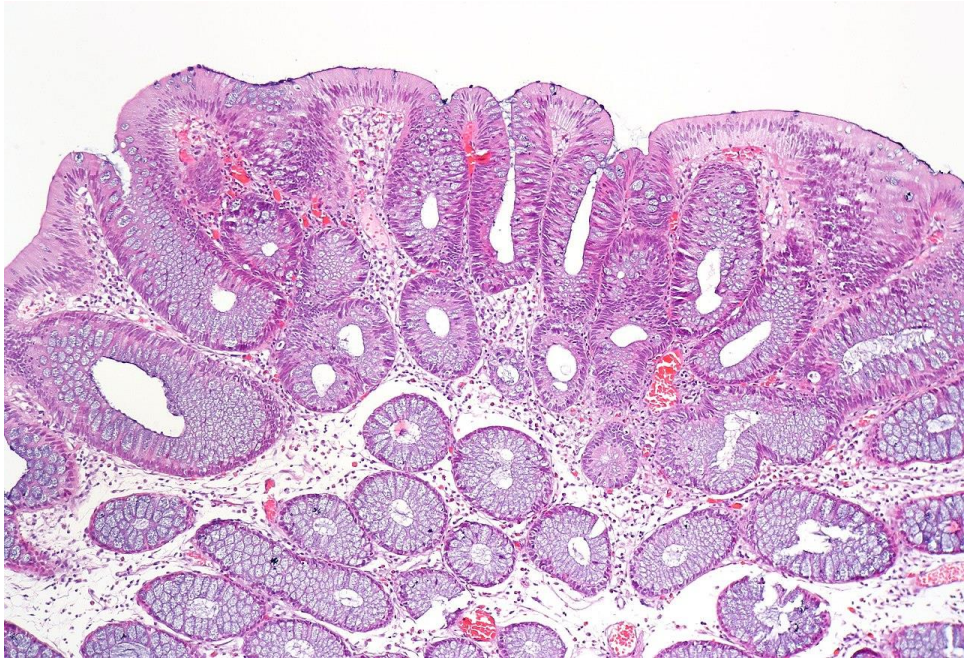

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Exceptions

- **Exceptions** to above general rules, i.e. malignant neoplasms with suffix - oma -
- **Melanomas**
- **Seminoma**
- **Hepatoma (hepatocellular Ca),**
- **Mesothelioma**
- **Lymphoma**

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Table 7.1 Classification of tumours.

	TISSUE OF ORIGIN	BENIGN	MALIGNANT
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	2. *Adult fibrous tissue*	Fibroma	Fibrosarcoma
	3. *Embryonic fibrous tissue*	Myxoma	Myxosarcoma
	4. *Cartilage*	Chondroma	Chondrosarcoma
	5. *Bone*	Osteoma	Osteosarcoma
	6. *Synovium*	Benign synovioma	Synovial sarcoma
	7. *Smooth muscle*	Leiomyoma	Leiomyosarcoma
	8. *Skeletal muscle*	Rhabdomyoma	Rhabdomyosarcoma
	9. *Mesothelium*	—	Mesothelioma
	10. *Blood vessels*	Haemangioma	Angiosarcoma
	11. *Lymph vessels*	Lymphangioma	Lymphangiosarcoma
	12. *Glomus*	Glomus tumour	—
	13. *Meninges*	Meningioma	Invasive meningioma
	14. *Haematopoietic cells*	—	Leukaemias
	15. *Lymphoid tissue*	Pseudolymphoma	Malignant lymphomas
	16. *Nerve sheath*	Neurilemmoma, Neurofibroma	Neurogenic sarcoma
	17. *Nerve cells*	Ganglioneuroma	Neuroblastoma
II.	MIXED TUMOURS		
	Salivary glands	Pleomorphic adenoma (mixed salivary tumour)	Malignant mixed salivary tumour
III.	TUMOURS OF MORE THAN ONE GERM CELL LAYER		
	Totipotent cells in gonads or in embryonal rests	Mature teratoma	Immature teratoma

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Malignant tumors

- Malignant tumors arising in **mesenchymal cell origin** are usually called **"sarcoma"**

- e.g. fibrosarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma

- Malignant tumors of **epithelial cell origin** are called **"carcinoma"**

Carcinoma may be further classified ->

- ❑ with glandular growth pattern, i.e. **adenocarcinoma**
- ❑ producing recognizable squamous cells of epithelium, i.e. **squamous cell carcinoma.**

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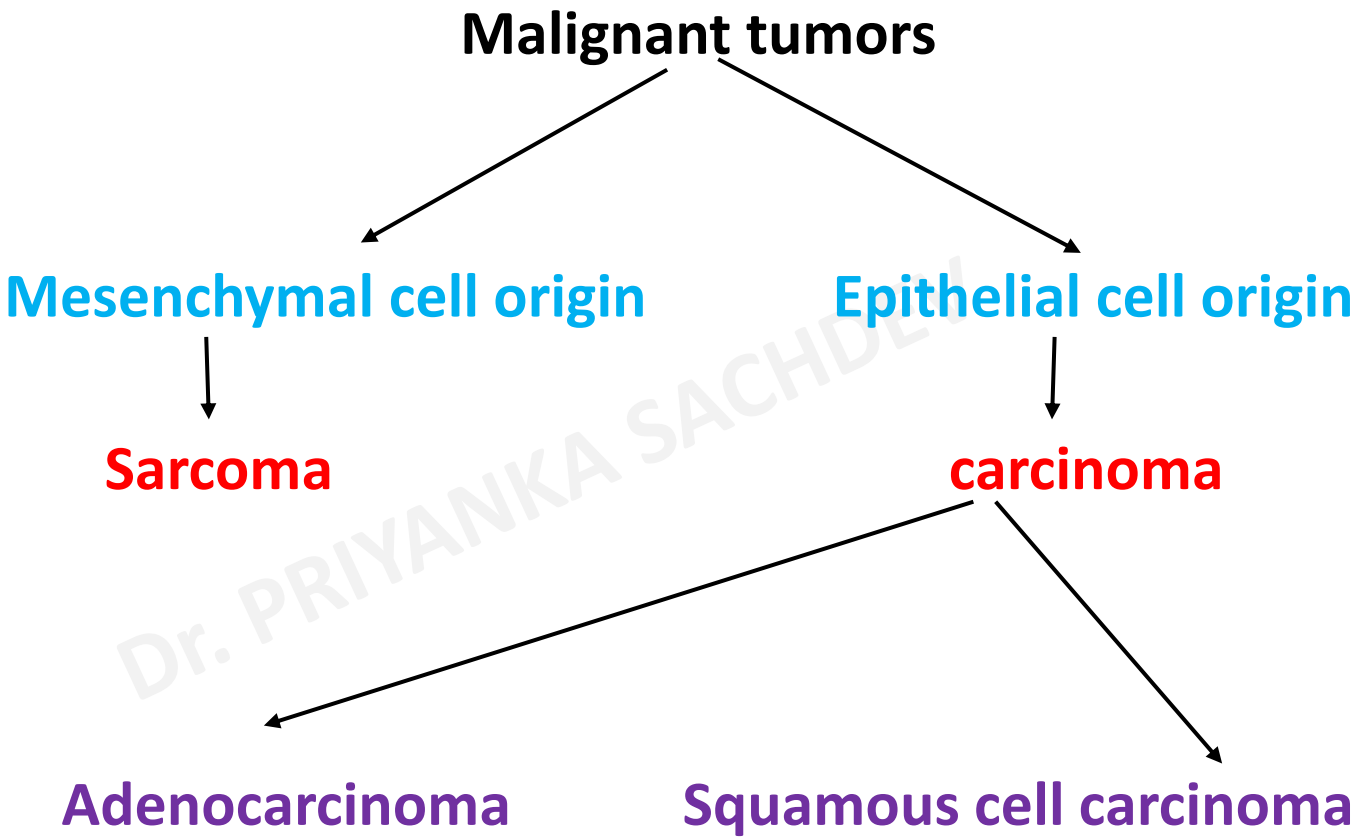

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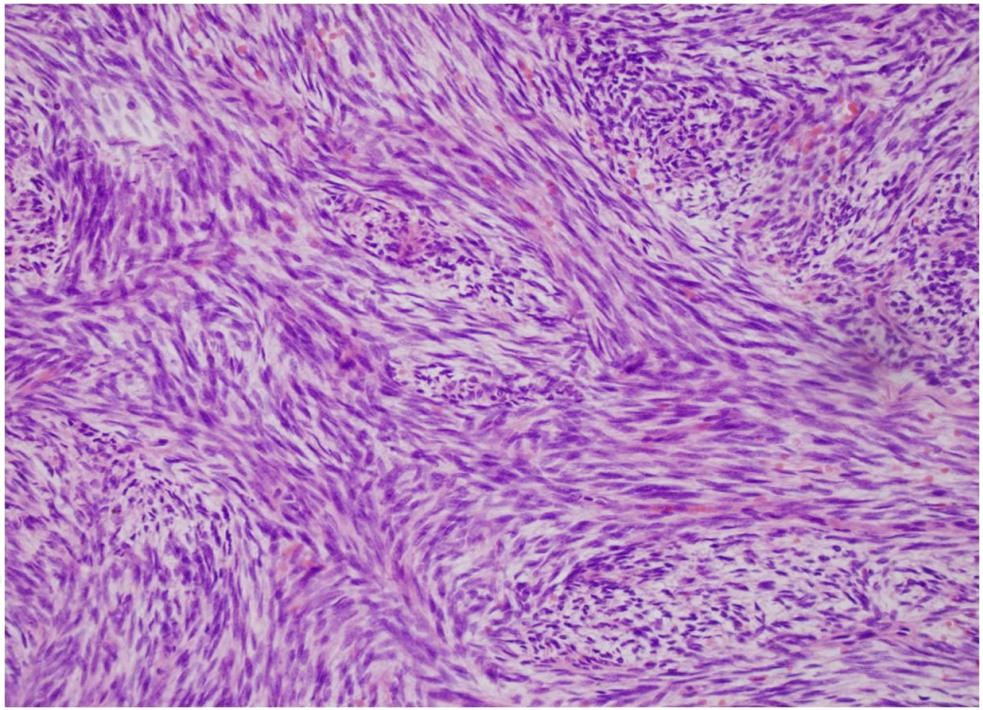

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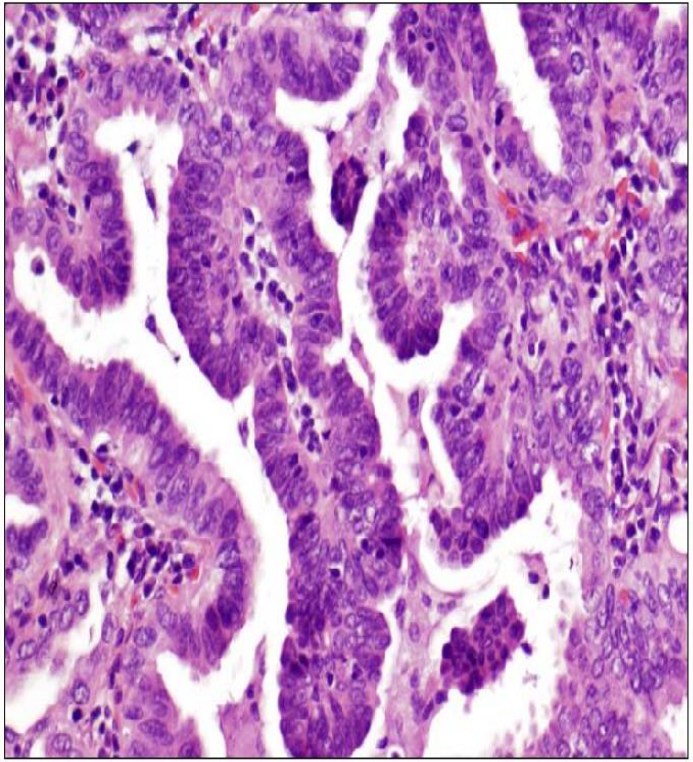
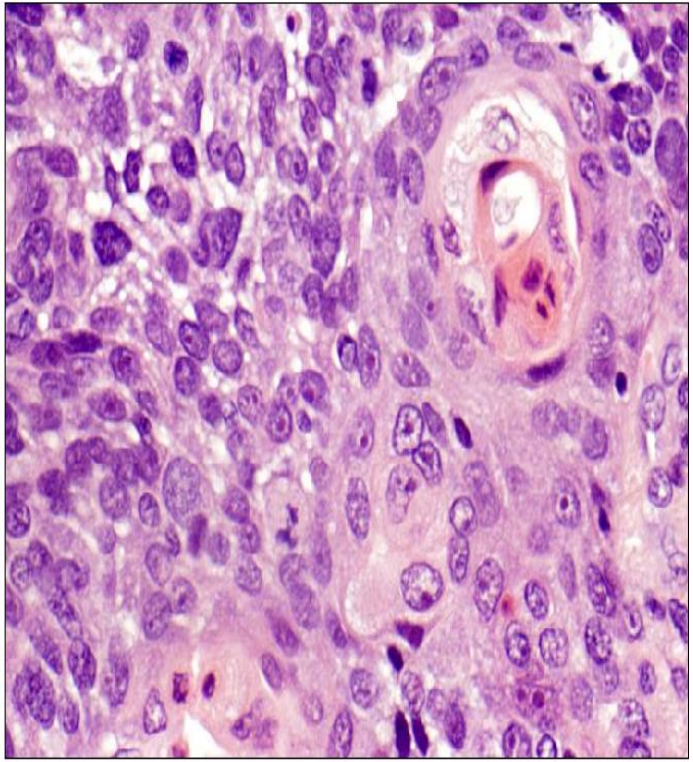
Adenocarcinoma



Squamous cell carcinoma



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SPECIAL CATEGORIES OF TUMOURS

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Mixed tumours

When **two types of tumours** are combined in the same tumour, it is called a mixed tumour.

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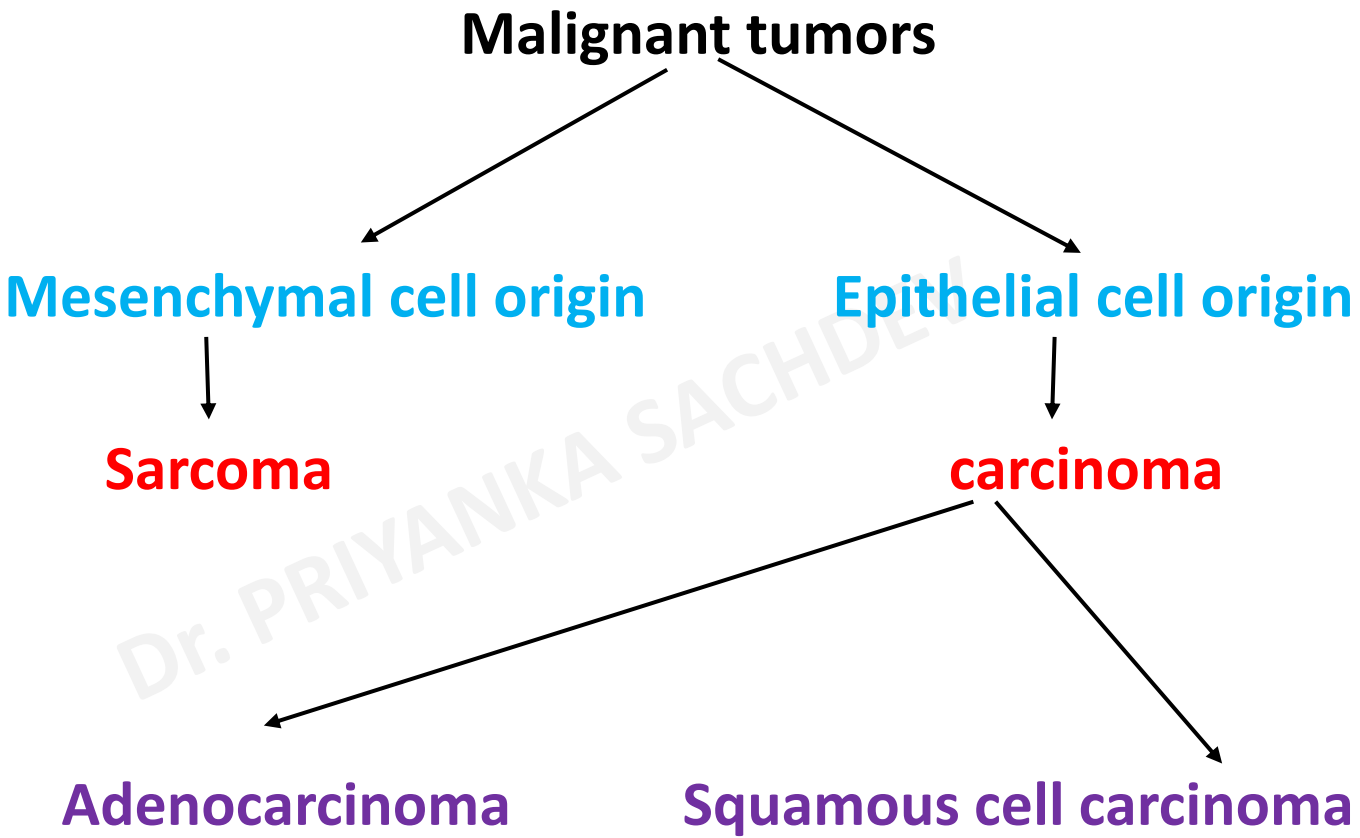
- example:

i) Adenosquamous carcinoma

ii) Carcinosarcoma



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Tetratoma

Tumors are composed of cells representative of a single germ layer.

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- Mixture from the **three germ cell layers** → ectoderm, mesoderm and endoderm known as teratoma

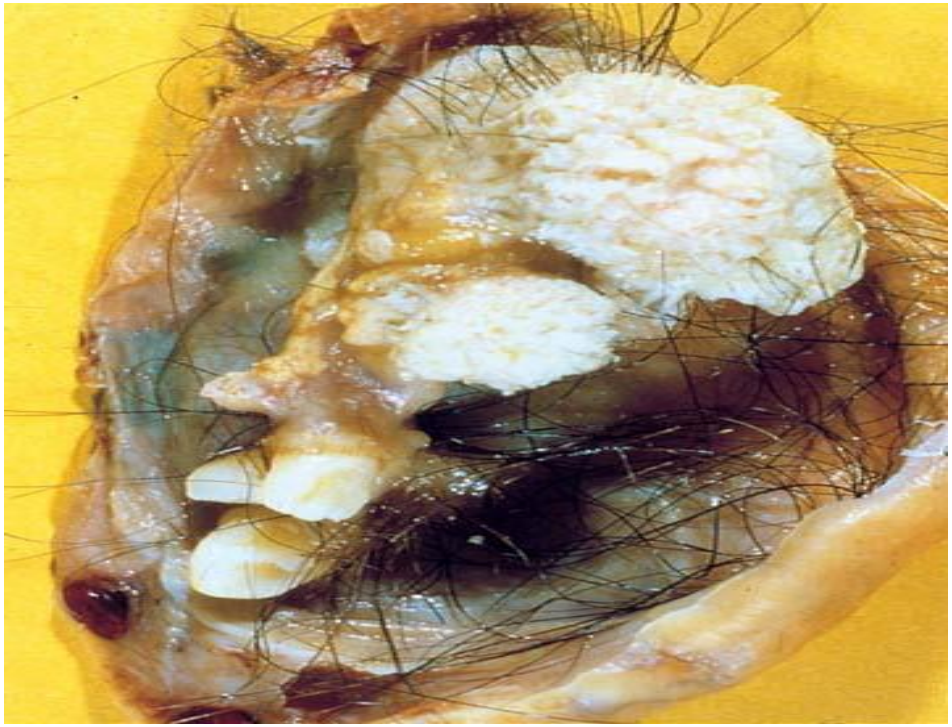

Figure 7-3 **A,** Gross appearance of an opened cystic teratoma of the ovary. Note the presence of hair, sebaceous material, and tooth. **B,** A microscopic view of a similar tumor shows skin, sebaceous glands, fat cells, and a tract of neural tissue *(arrow)*.

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Blastomas (Embryomas)

- Arise from **embryonal / Primitive cells**
- These tumours occur more frequently in **infants and children** (under 5 years of age).
- eg: neuroblastoma, nephroblastoma (Wilms' tumour), hepatoblastoma, retinoblastoma, medulloblastoma, pulmonary blastoma.

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Not actual tumors (neoplasms)

1.Hamartoma

2.Choristoma

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Hamartoma

- **It is a focal developmental malformation**
- It represents a mass of disorganized but mature specialized cells indigenous to the particular site
- e.g. hamartoma of the lung consists of mature cartilage, mature smooth muscle and epithelium.

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Choristoma

- **Ectopic islands of normal tissue.**
- Thus, choristoma is heterotopia but is not a true tumour
- Eg. Pancreatic tissue in mucosa of small intestine

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- **Normally arranged tissue at abnormal (ectopic) site**: **Choristoma**

- **Abnormally arranged tissue at normal site**: **Hamartoma**

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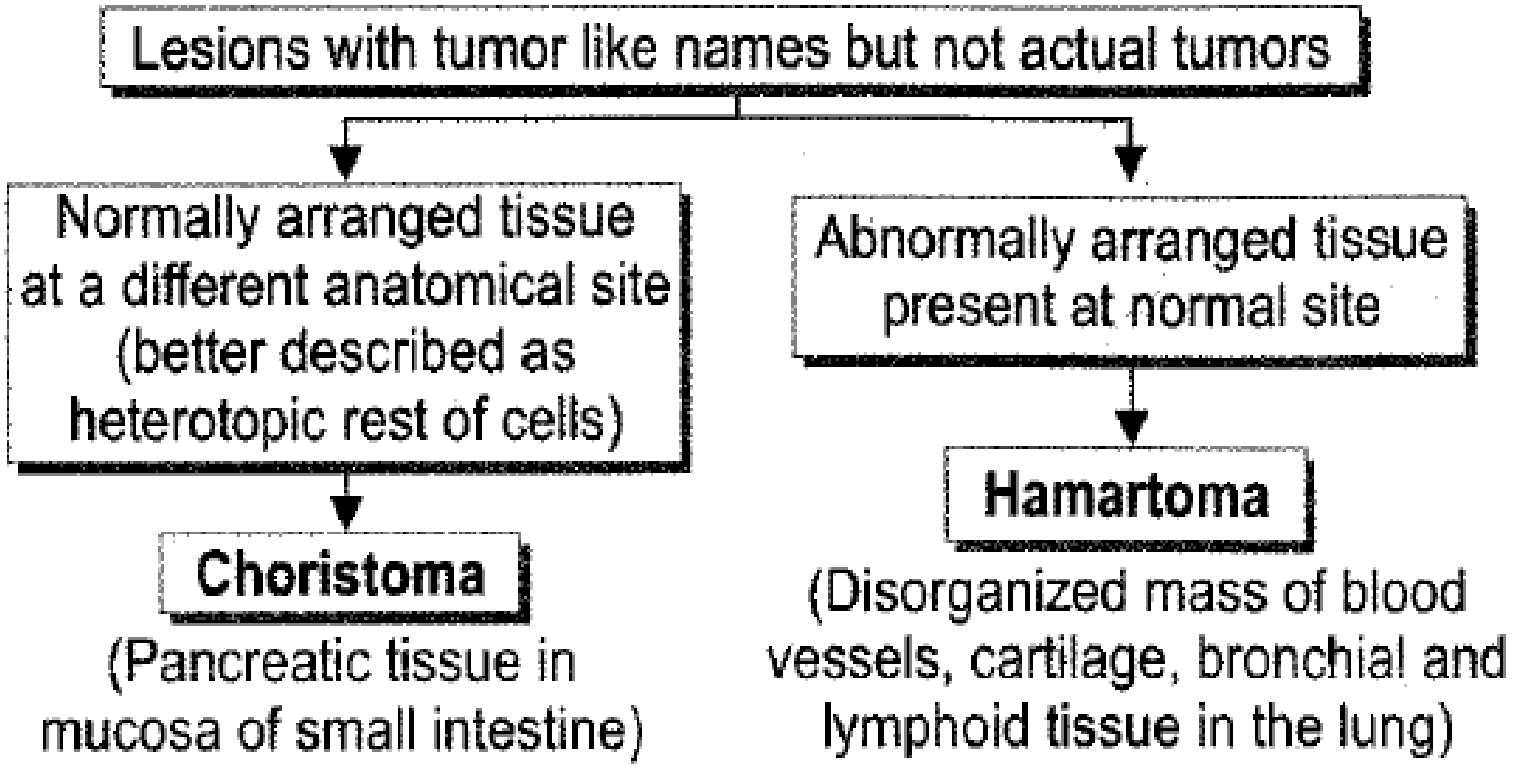
Lesions with tumor like names but not actual tumors
Normally arranged tissue at a different anatomical site (better described as heterotopic rest of cells)
Choristoma
(Pancreatic tissue in mucosa of small intestine)
Abnormally arranged tissue present at normal site
Hamartoma
(Disorganized mass of blood vessels, cartilage, bronchial and lymphoid tissue in the lung)

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Carcinoma originating from glands is called -

a) Basal cell carcinoma
b) Squamous cell carcinoma
c) Adenocarcinoma
d) Fibrosarcoma

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Tumor containing cells of all three germ layers is called -

a) Leiomyoma
b) Squamous cell carcinoma
c) Adenocarcinoma
d) Teratoma

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D

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Hamartoma is -

a) Malignant tumor
b) Metastatic tissue
c) Development malformation
d) Hemorrhage in vessel

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Ectopic rest of normal tissue is known as -

a) Choristoma
b) Hamartoma
c) Pheudotumor
d) Lymphoma

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A

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Excessive fibrosis in tumor in called -

a) Anaplasia
b) Metaplasia
c) Desmoplasia
d) Dysplasia

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c

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Hamartoma is:

(a) Proliferation of cells in foreign site
(b) Proliferation of native cells in tissue
(c) Malignant condition
(d) Acquired condition

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B

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Overgrowth of a skin structure at a localised region is:

(a) Hamartoma
(b) Malignant tumor
(c) Choristoma
(d) Polyp

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A

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Hamartoma refers to:

A. Tumour differentiating towards more than one cell line

B. Tumour arising from totipotent cells

C. Mass of disorganised but mature cells indigenous to the part

D. Mass of ectopic rests of normal tissue

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
2. Clinical features
3. Gross features
4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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1. Rate of growth

1.Malignant tumour cells have→

- **Increased mitotic rate (less doubling time) and slower death rate** ie. cell production exceeds the cell loss.
- Sometimes tumour cells in the centre of the tumour do not receive adequate nourishment and undergo ischaemic necrosis.

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2. Rate of growth of malignant tumour is directly proportionate to the **degree of differentiation.**

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- Poorly differentiated tumours show aggressive growth as compared to well differentiated tumours.

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- 3. Usually, **10^9 cells** produce a clinically detectable tumor.

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
2. Clinical features
3. Gross features
4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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2. CLINICAL FEATURES

Benign tumours

- slow growing
- May remain asymptomatic (e.g. subcutaneous lipoma)
- May produce serious symptoms (e.g. meningioma in the CNS)

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Malignant tumours

- Grow rapidly
- May ulcerate on the surface,
- Invade locally into deeper tissues,
- May spread to distant sites (metastasis)
- Systemic features such as weight loss, anorexia and anaemia.

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CHARACTERISTICS OF TUMOURS

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3. GROSS FEATURES

Benign tumours

- Spherical or ovoid in shape.
- Encapsulated or well-circumscribed
- Freely movable
- More firm and uniform
- **Surrounding tissue compressed**

Malignant tumours

- Irregular in shape
- Poorly-circumscribed
- Extend into the adjacent tissues.
- Sarcomas typically have fishflesh like consistency while carcinomas are generally firm
- **Surrounding tissue invaded**

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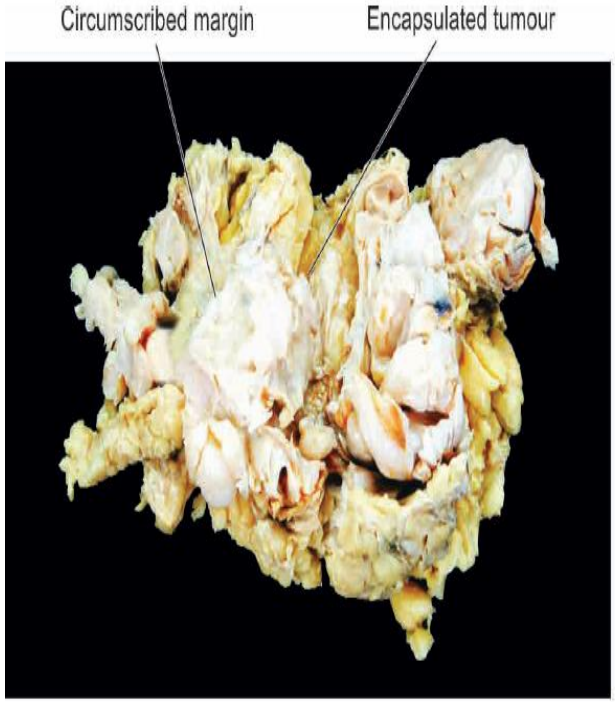
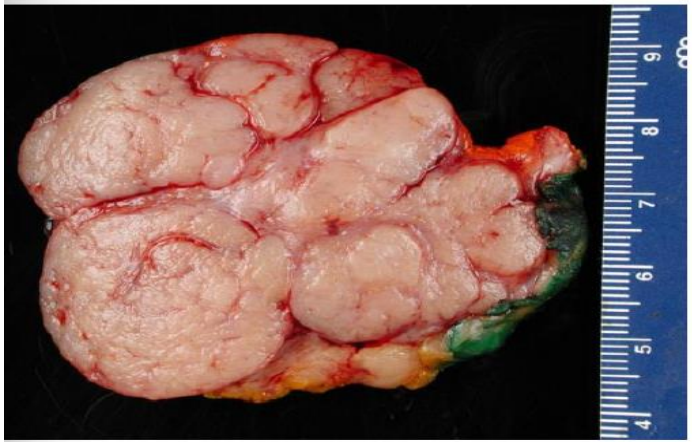


A. FIBROADENOMA BREAST

B. INFILTRATING CARCINOMA BREAST

Benign vs. Malignant Breast Tumors

Gross Features



Fibroadenoma

Adenocarcinoma

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CHARACTERISTICS OF TUMOURS

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4. MICROSCOPIC FEATURES

- Lack of differentiation

OR

- Presence of Anaplasia

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Differentiation

Differentiation is defined as the **extent of morphological and functional resemblance of tumour cells to corresponding normal cells**.

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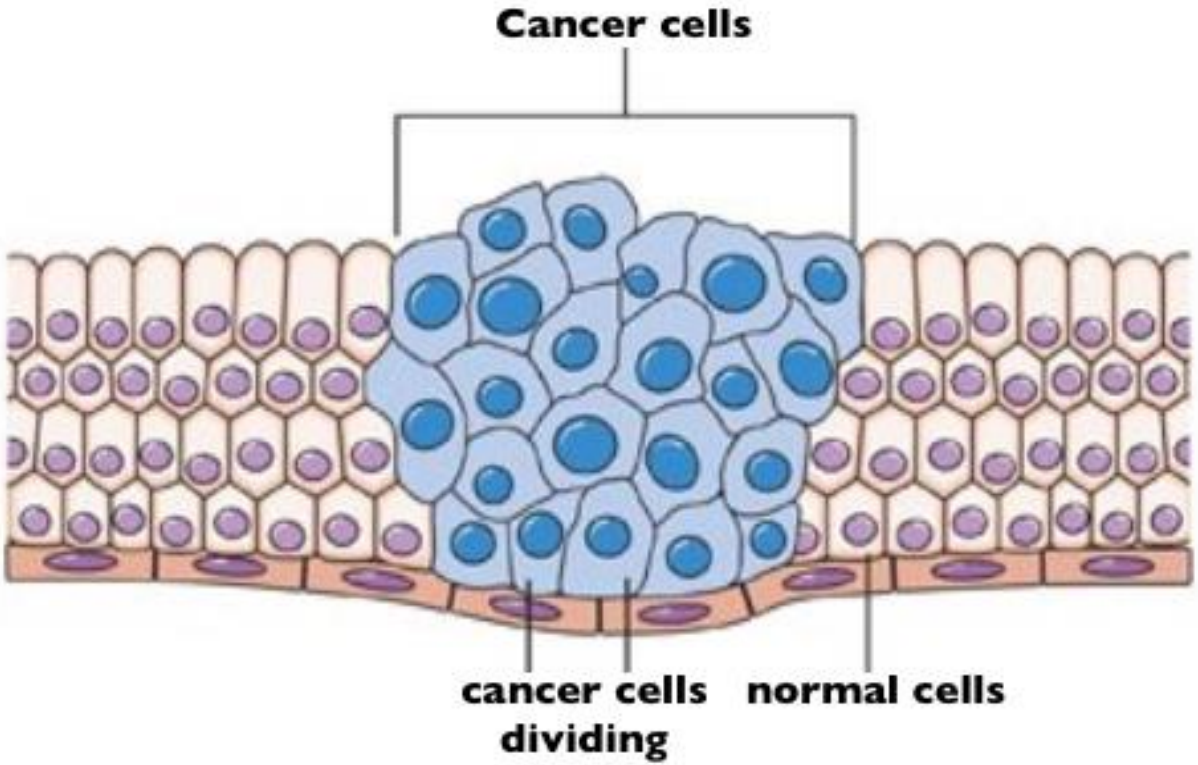
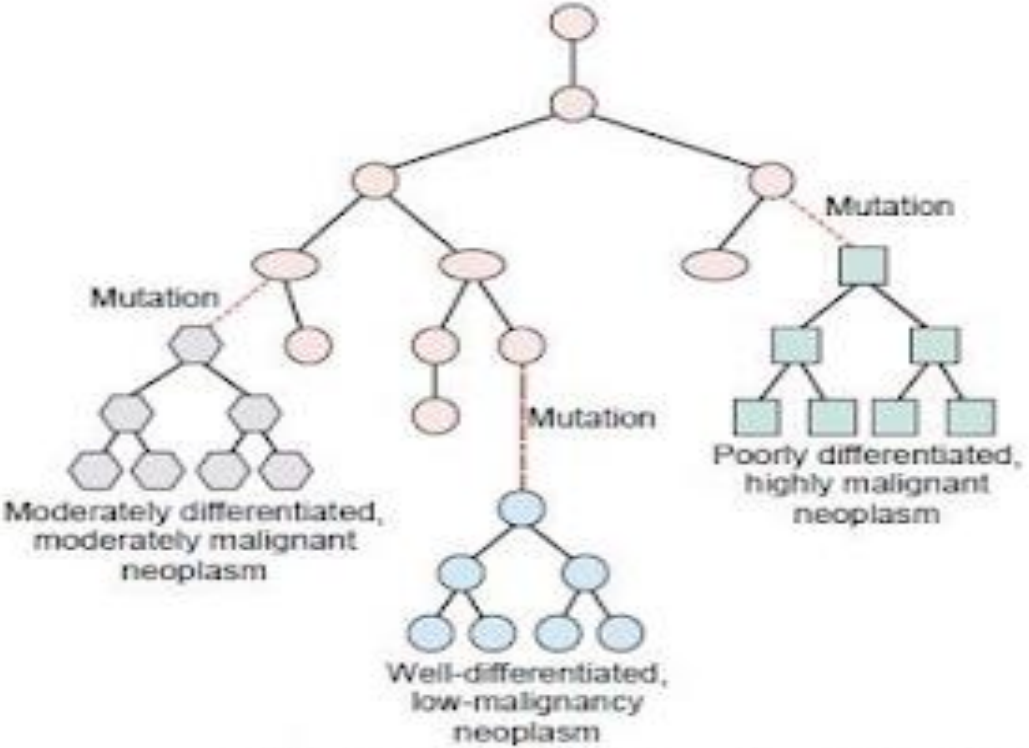
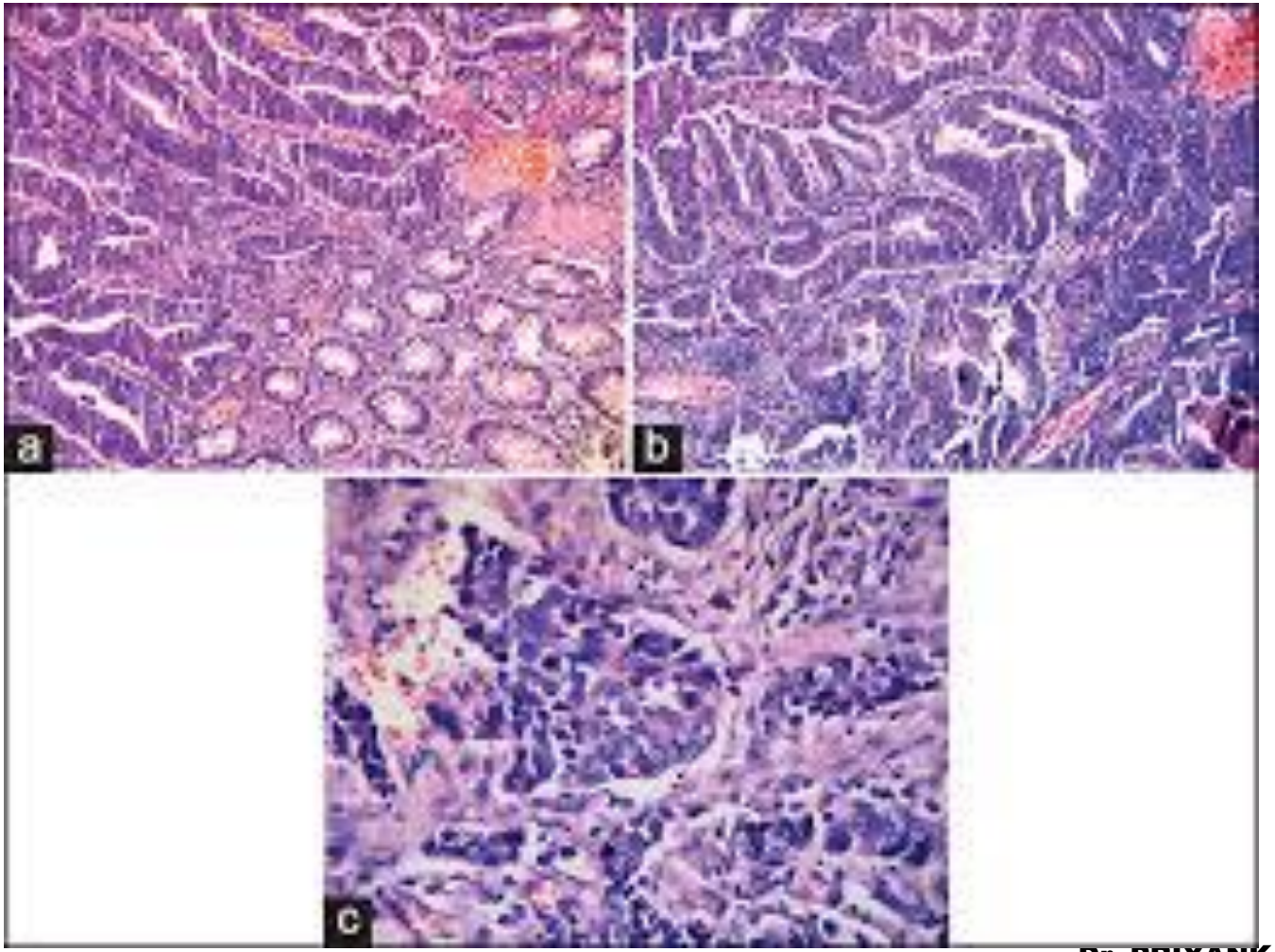
1. If resemblance of tumor cell to normal cell is more → '**well-differentiated'**
2. If resemblance of tumor cell to normal cell is moderate → '**moderately -differentiated'**
3. If resemblance of tumor cell to normal cell is minimal → '**poorly-differentiated'**
4. If no resemblance of tumor cell to normal cell is more → '**Undifferentiated'**


Cancer cells
cancer cells dividing
normal cells



Mutation of a cell line. Generally, mutations that occur early in the differentiation process result in poorly differentiated neoplasms and those that appear late in the differentiation process result in relatively well-differentiated neoplasms.


a
b
c

Anaplasia

- **Anaplasia is lack of differentiation**
- Characteristic feature of malignant tumours
- Anaplasia is considered as a **hallmark of malignant transformation,**
- It is **irreversible**

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- Depends upon the degree of differentiation i.e. poorly differentiated malignant tumours have high degree of anaplasia.

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Features of anaplasia

1. Loss of polarity
2. Pleomorphism
3. N:C ratio
4. Anisonucleosis
5. Hyperchromatism
6. Nucleolar changes
7. Mitotic figures
8. Tumor giant cells
9. Cytoplasm increased mucin
10. DNA anuploidy

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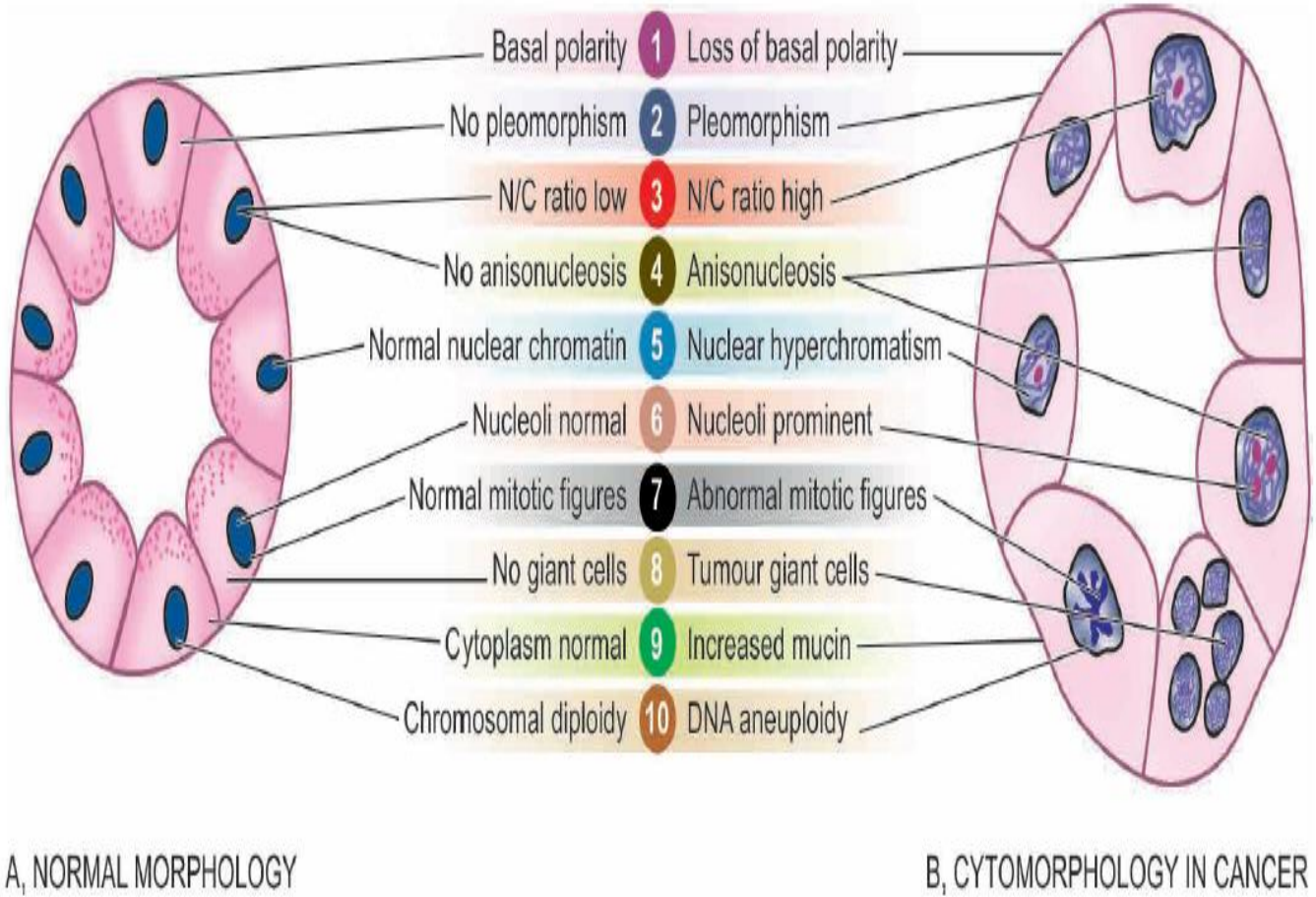
Basal polarity
1
Loss of basal polarity
No pleomorphism
2
Pleomorphism
N/C ratio low
3
N/C ratio high
No anisonucleosis
4
Anisonucleosis
Normal nuclear chromatin
5
Nuclear hyperchromatism
Nucleoli normal
6
Nucleoli prominent
Normal mitotic figures
7
Abnormal mitotic figures
No giant cells
8
Tumour giant cells
Cytoplasm normal
9
Increased mucin
Chromosomal diploidy
10
DNA aneuploidy
A, NORMAL MORPHOLOGY
B, CYTOMORPHOLOGY IN CANCER

1. Loss of polarity

- Normally, the nuclei of epithelial cells are oriented along the basement membrane which is termed as basal polarity.
- Tumour cells lose their basal polarity so that **the nuclei tend to lie away from the basement membrane**

2. Pleomorphism

- **Variation in size and shape of the tumour cells.**

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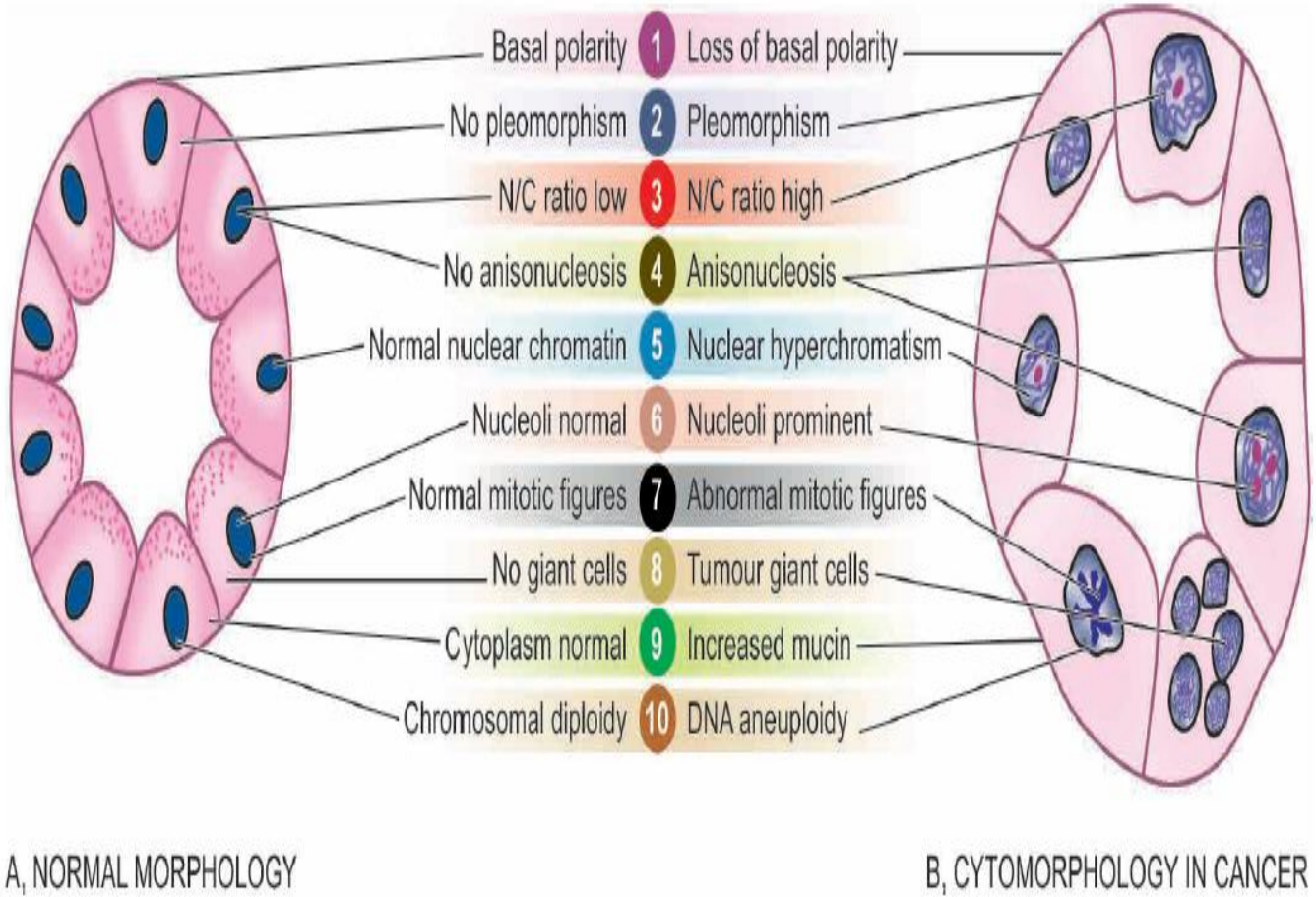
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A, NORMAL MORPHOLOGY
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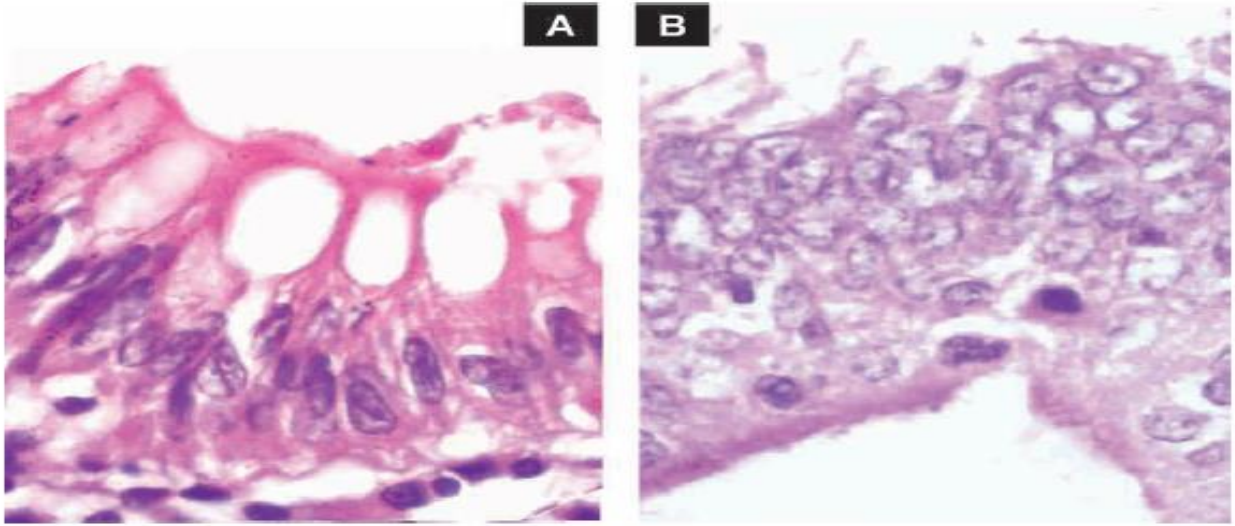

Figure 7.5 Microscopic appearance of loss of nuclear polarity (B) contrasted with normal basal polarity in columnar epithelium (A). The basement membrane is intact in both.

- **N:C ratio**→ **Nuclei are enlarged disproportionate to the cell size** so that the nucleocytoplasmic ratio is increased. In normal cells, the nuclear cytoplasmic (or N: C) ratio is 1:4 whereas it becomes 1:1 in anaplastic cells.

4. Anisonucleosis → **the nuclei show variation in size and shape** in malignant tumour cells

- ***5.*** **Hyperchromatism** → Increased nuclear material or DNA is responsible for **dark staining of the cells** called hyperchromasia.

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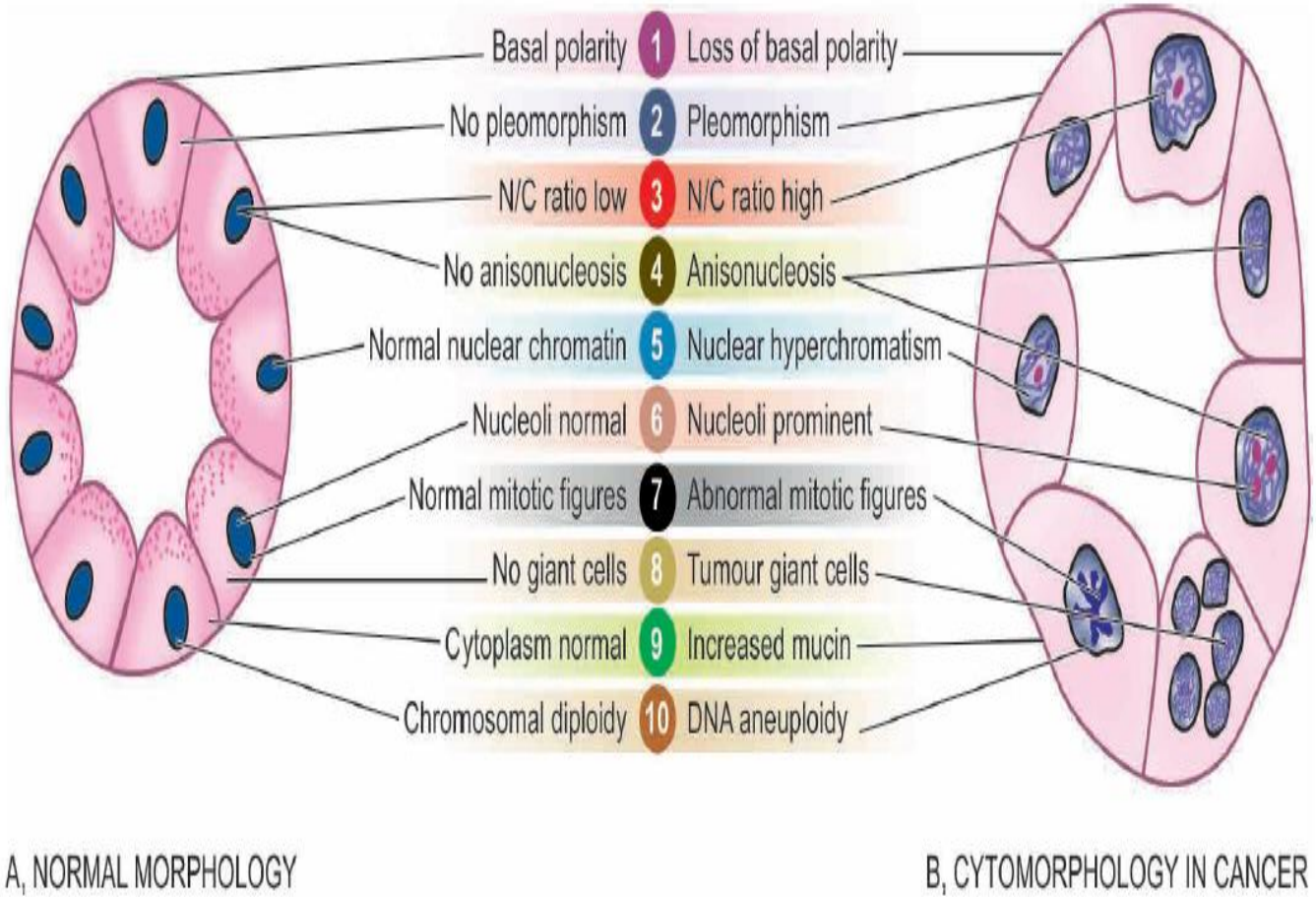
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Cytoplasm normal
9
Increased mucin
Chromosomal diploidy
10
DNA aneuploidy
A, NORMAL MORPHOLOGY
B, CYTOMORPHOLOGY IN CANCER

6. Nucleolar changes

- Malignant cells have a **prominent nucleolus** or nucleoli in the nucleus
- This may be demonstrated as Nucleolar Organiser Region (NOR) by silver (Ag) staining called AgNOR material.

7. Mitotic figures

- Tumour cells show **large number of normal or abnormal mitoses**

8. Tumor giant cells

- **Multinucleate tumour giant cells** important feature of malignant cells

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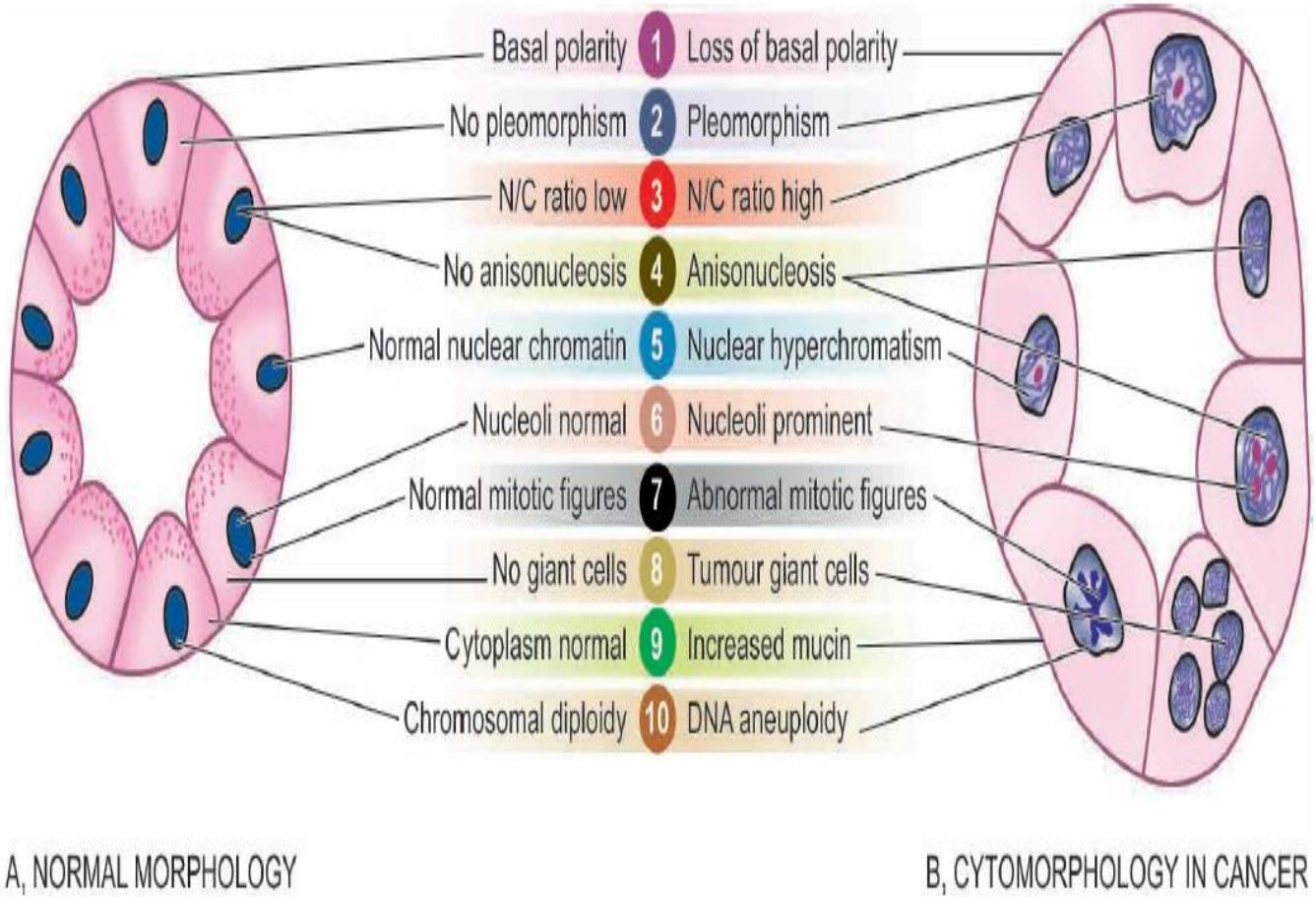
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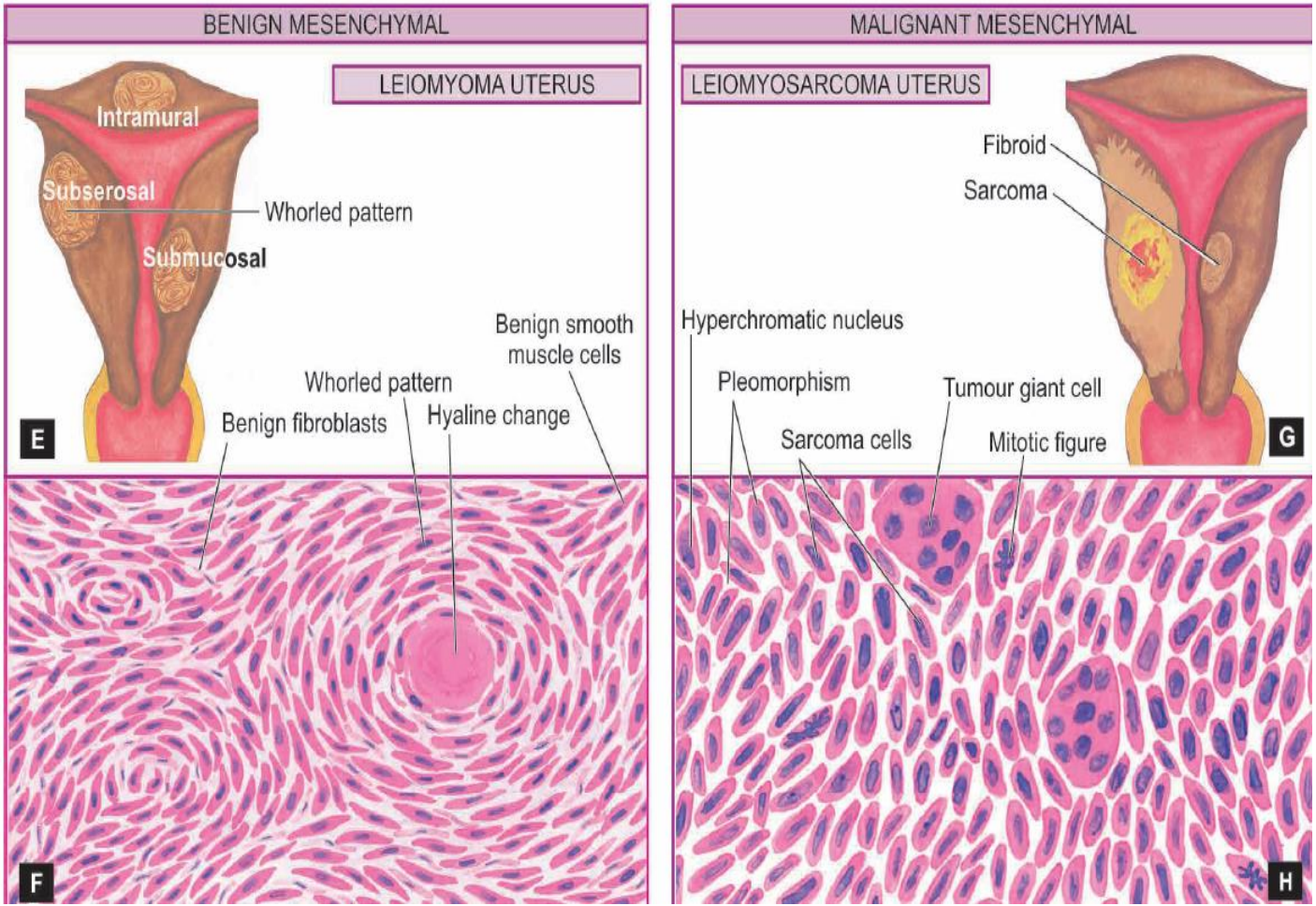
A, NORMAL MORPHOLOGY
B, CYTOMORPHOLOGY IN CANCER


BENIGN MESENCHYMAL
LEIOMYOMA UTERUS
Intramural
Subserosal
Submucosal
Whorled pattern
E
Benign smooth muscle cells
Whorled pattern
Hyaline change
Benign fibroblasts
F
MALIGNANT MESENCHYMAL
LEIOMYOSARCOMA UTERUS
Fibroid
Sarcoma
G
Hyperchromatic nucleus
Pleomorphism
Tumour giant cell
Sarcoma cells
Mitotic figure
H

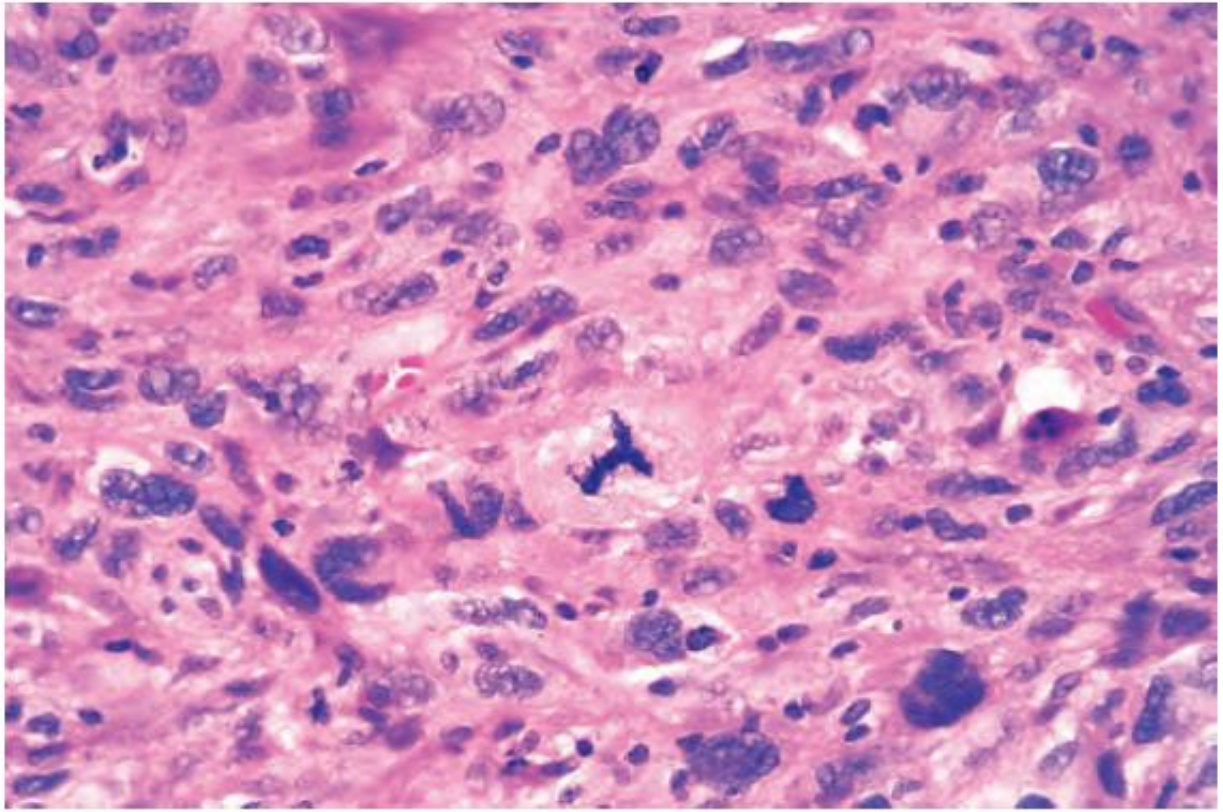


Figure 7-8 Anaplastic tumor showing cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

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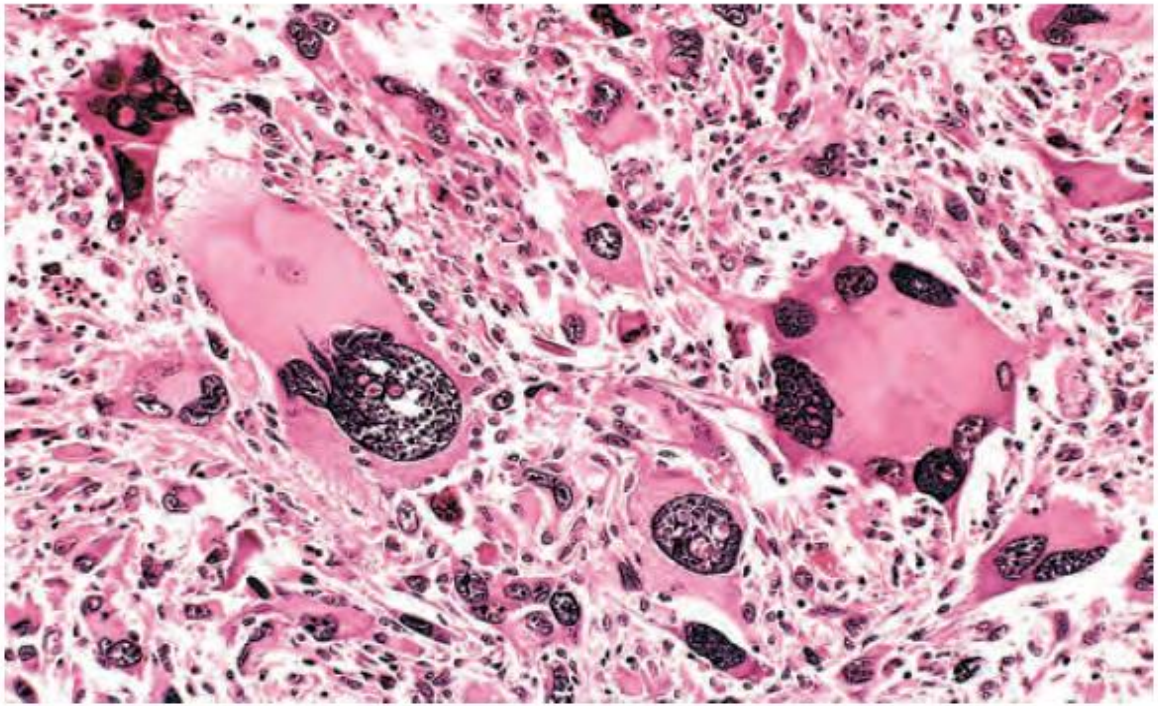
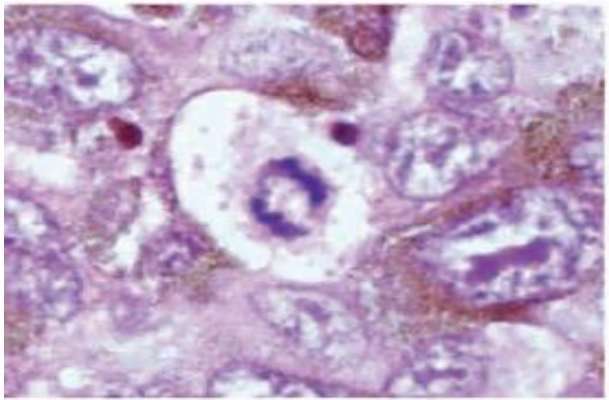
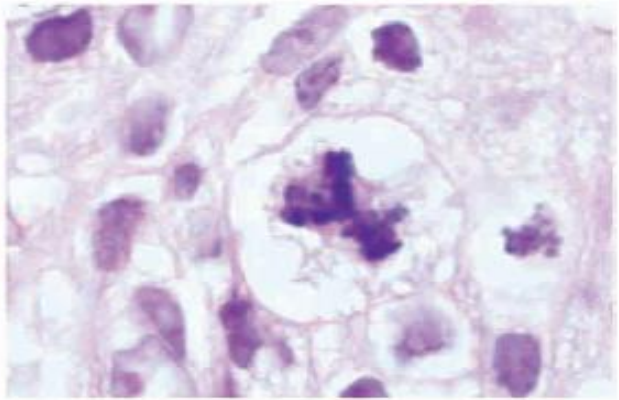


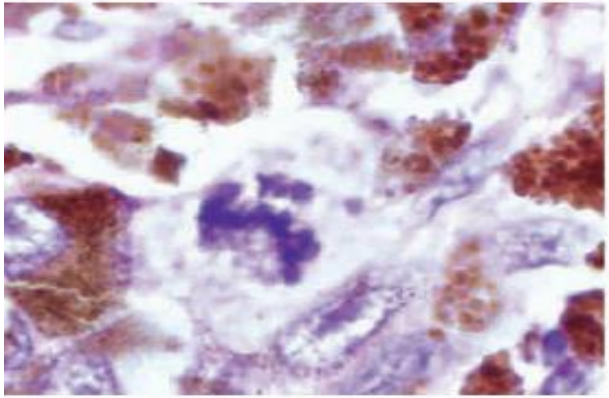
Figure 7-9 Pleomorphic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei, and tumor giant cells. (Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)

BIPOLAR MITOSIS

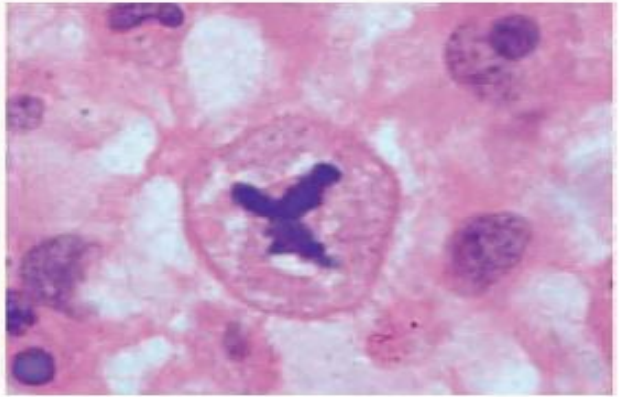


ABNORMAL MITOSIS





ABNORMAL MITOSIS



ABNORMAL MITOSIS

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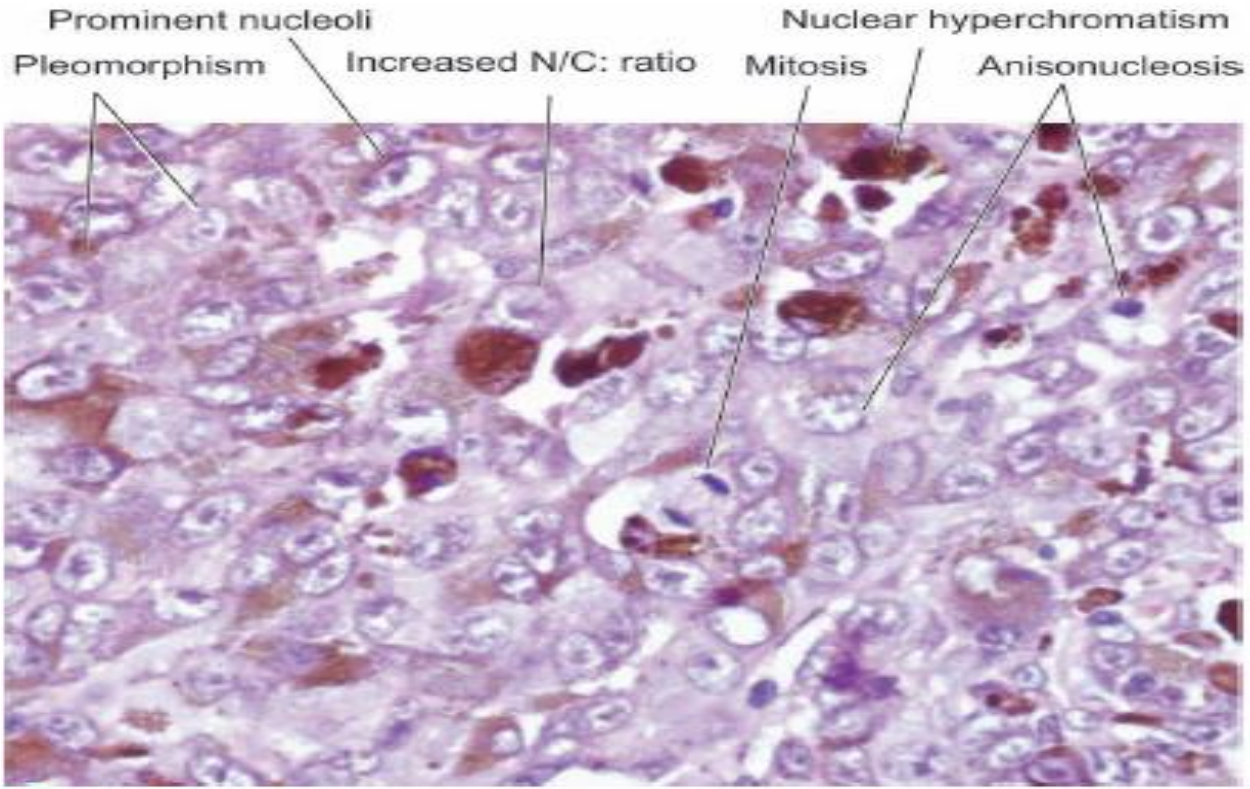

Figure 7.6 Nuclear features of malignant cells in malignant melanoma—pleomorphism, anisonucleosis, increased N/C: ratio, nuclear hyperchromatism and prominent nucleoli.

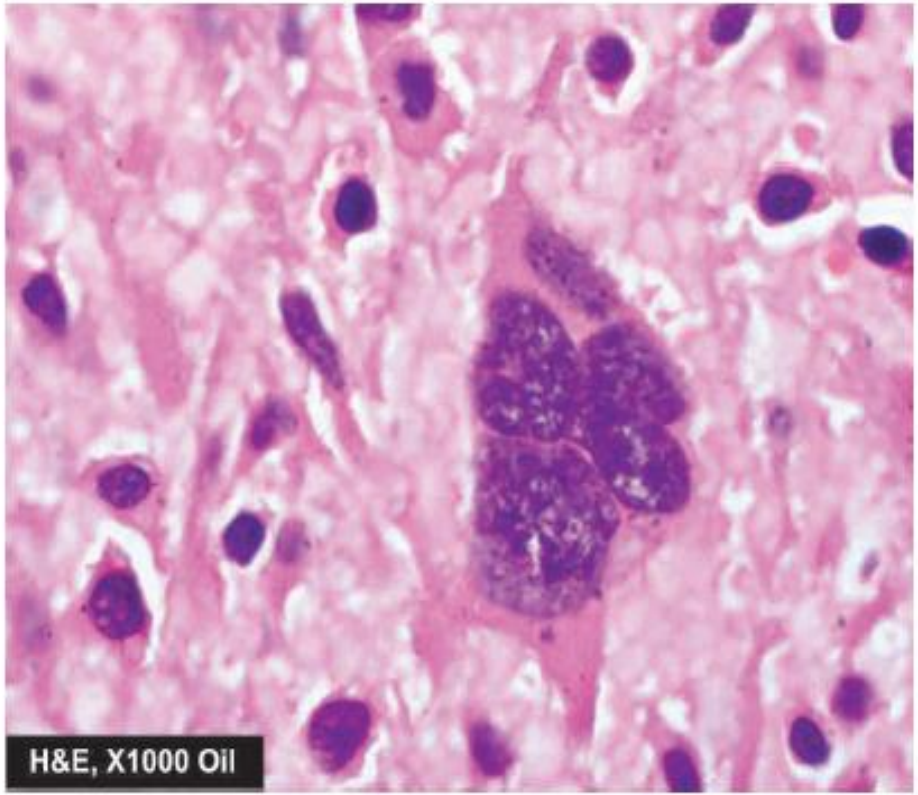

Figure 7.8 A multinucleate tumour giant cell in osteosarcoma.

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REMEMBER

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Following conditions are related to ditterentiation→

- **1) Metaplasia**
- **2) Dysplasia**
- **3) Anaplasia**

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- **METAPLASIA** → differentiation is not lost, rather it **changes** from one lineage to another
- It is **reversible**

- **DYSPLASIA** →There is **disordered** differentiation and maturation.
- It is **parially reversible**

- **ANAPLASIA**→ **lack** of differentiation
- It is **irreversible**

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Differentiating features of metaplasia , anaplasia and dysplasia

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Feature	Metaplasia	Dysplasia	Anaplasia
Definition	Reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type	A change having loss in the uniformity of the individual cells and loss of architectural orientation	An *absence of differentiation* (extent to which neoplastic cells resemble normal cells both morphologically and functionally)
Pleomorphism (variation in the size and shape of cells/nuclei)	Absent	**Present**[Q] in low grade	**Present**[Q] in high grade
Reversibility	Reversible[Q]	**Reversible in early stages** (irreversible if whole epithelium is involved)	Irreversible[Q]
N:C ratio	Normal (1:4)	Increased (↑)	Increased (↑↑↑)
Hyperchromatism	Absent	Present (small degree)	Present (high degree)
Mitotic figures	Absent/minimal at normal places	**Typical mitotic figures**[Q] present at abnormal places	**Atypical mitotic figures**[Q] (multipolar spindles) present at abnormal places
Other features (Tumor giant cells[Q], hemorrhage, necrosis)	Absent	Absent	**Present**[Q]
Example	Barret's esophagus, myositis ossificans	Cervical dysplasia of squamous cells	Carcinoma of the cervix, carcinoma esophagus

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- **Dysplasia** is a **benign condition** (premalignant)

- **Anaplasia** is hallmark of **malignancy**

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
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4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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	FEATURE	BENIGN	MALIGNANT
I.	CLINICAL AND GROSS FEATURES		
	1. *Boundaries*	Encapsulated or well-circumscribed	Poorly-circumscribed and irregular
	2. *Surrounding tissue*	Often compressed	Usually invaded
	3. *Size*	Usually small	Often larger
	4. *Secondary changes*	Occur less often	Occur more often
II.	MICROSCOPIC FEATURES		
	1. *Pattern*	Usually resembles the tissue of origin closely	Often poor resemblance to tissue of origin
	2. *Basal polarity*	Retained	Often lost
	3. *Pleomorphism*	Usually not present	Often present
	4. *Nucleo-cytoplasmic ratio*	Normal	Increased
	5. *Anisonucleosis*	Absent	Generally present
	6. *Hyperchromatism*	Absent	Often present
	7. *Mitoses*	May be present but are always typical mitoses	Mitotic figures increased and are generally atypical and abnormal
	8. *Tumour giant cells*	May be present but without nuclear atypia	Present with nuclear atypia
	9. *Chromosomal abnormalities*	Infrequent	Invariably present
	10. *Function*	Usually well maintained	May be retained, lost or become abnormal
III.	GROWTH RATE	Usually slow	Usually rapid
IV.	LOCAL INVASION	Often compresses the surrounding tissues without invading or infiltrating them	Usually infiltrates and invades the adjacent tissues
V.	METASTASIS	Absent	Frequently present
VI.	PROGNOSIS	Local complications	Death by local and metastatic complications

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Criteria	Benign	Malignant (cancer)
Differentiation	Well differentiated	Well differentiated to undifferentiated (anaplastic)
Growth limits	Limited, encapsulated	Unrestricted, no surrounding capsule
Growth rate	Usually slow	Often rapid, but can be slow
Invasivness	Non-invasive	Invasive
Metastasis	Non-metastatic	Metastatic
Mitotic figures	Rare	**Atypical, with increased number** *(PGI 98)*
Cell size & shape	Uniform	Pleomorphism
Nuclear to cytoplasmic ratio	Normal (1:4 to 1:6)	Increased (1:1)
Stroma	Abundant	Often scanty
Cell orientation (Polarity)	Normal	Disorganized (loss of polarity)
Nuclear chromatin	Normal	Hyperchromatasla
Blood supply	Adequate	Often inadequate thus areas of necrosis

POLLS 2

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Scan or Click to watch
Neoplasia E01

Scan or Click to watch
Renal Pathology E02

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Lack of differentiation is called -

a) Anaplasia
b) Dysplasia
c) Metaplasia
d) Hyperplasia

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A

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Reversible loss of polarity with abnormality in size and shape of cells is known as -

a) Metaplasia
b) Dysplasia
c) Hyperplasia
d) Anaplasia

Dr. PR

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B

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How do you differentiate CA in situ from invasive CA-

a) Penetration of Basement membrane
b) Number of mitotic cells
c) Metastasis
d) Nuclear plemorphism

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A

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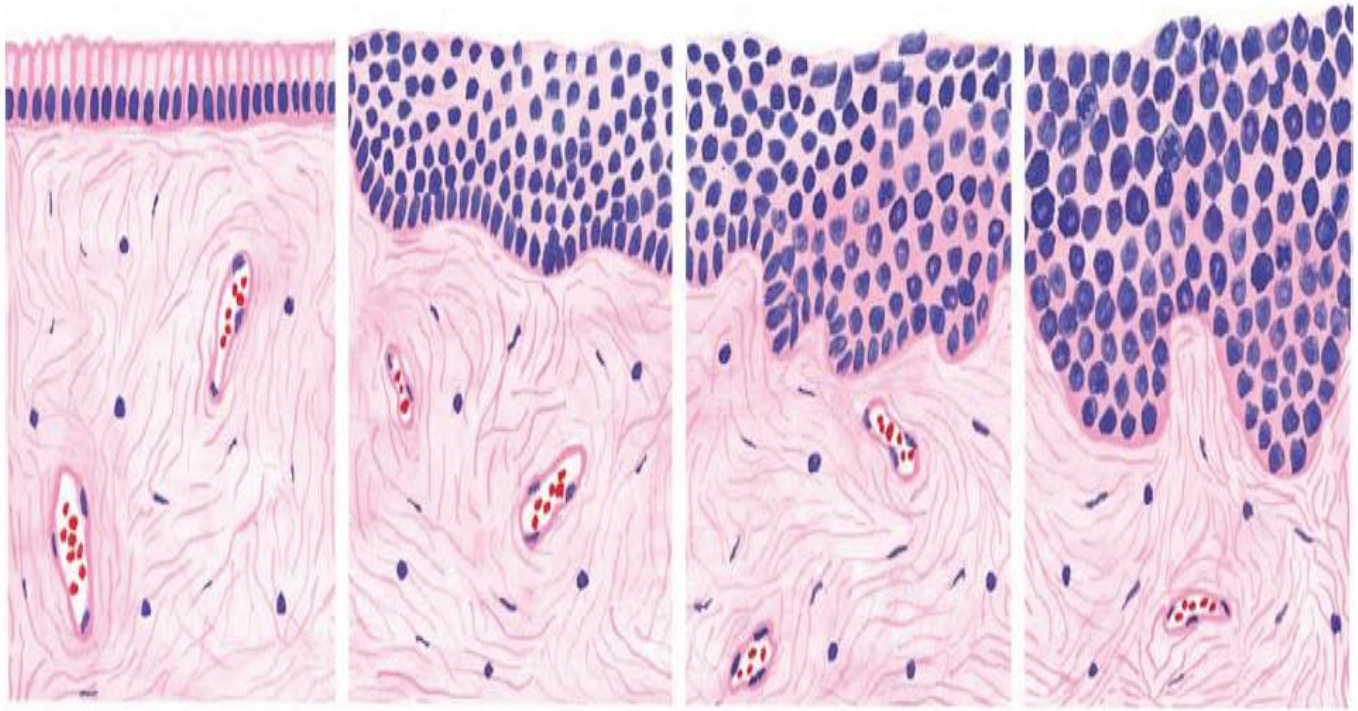

A, NORMAL ENDOCERVICAL EPITHELIUM

B, SQUAMOUS METAPLASIA

C, DYSPLASIA

D, CARCINOMA *IN SITU*

Earliest changes of neoplastic transformation as seen at a microscopic level is called:

(a) Hyperplasia
(b) Metaplasia
(c) Dysplasia
(d) Carcinoma in situ

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c

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A lesion 3 cm away from gastroesophageal junction contain columnar epithelium, such a type of lesion is:

(a) Metaplasia
(b) Hyperplasia
(c) Dysplasia
(d) Anaplasia

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A

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
2. Clinical features
3. Gross features
4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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5. SPREAD OF TUMOURS

1.Local invasion (direct spread)

2.Metastasis (distant spread)

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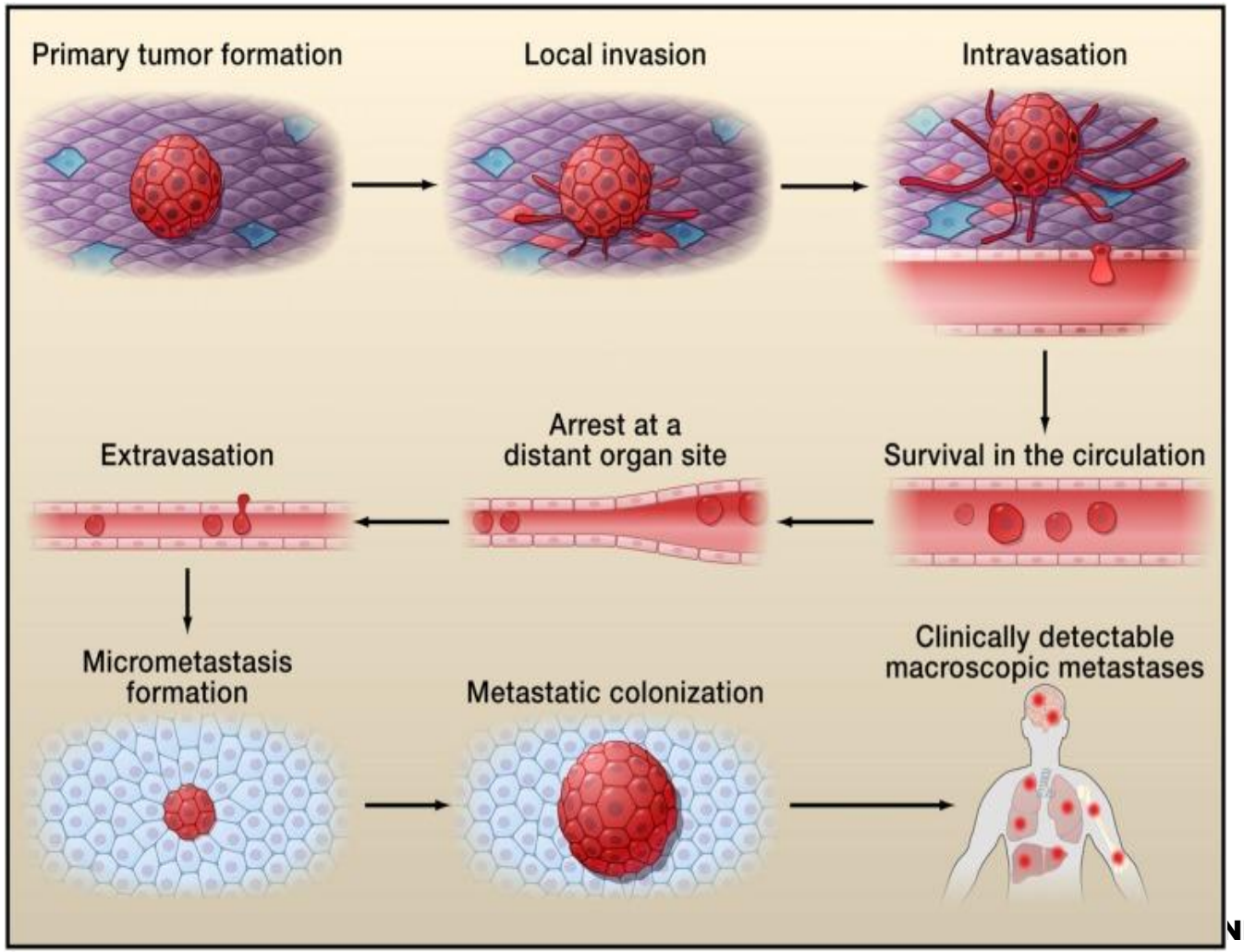
- Invasiveness and metastasis are the two other most important features to distinguish malignant from benign tumours.


Primary tumor formation
Local invasion
Intravasation
Survival in the circulation
Arrest at a distant organ site
Extravasation
Micrometastasis formation
Metastatic colonization
Clinically detectable macroscopic metastases

LOCAL INVASION (DIRECT SPREAD)

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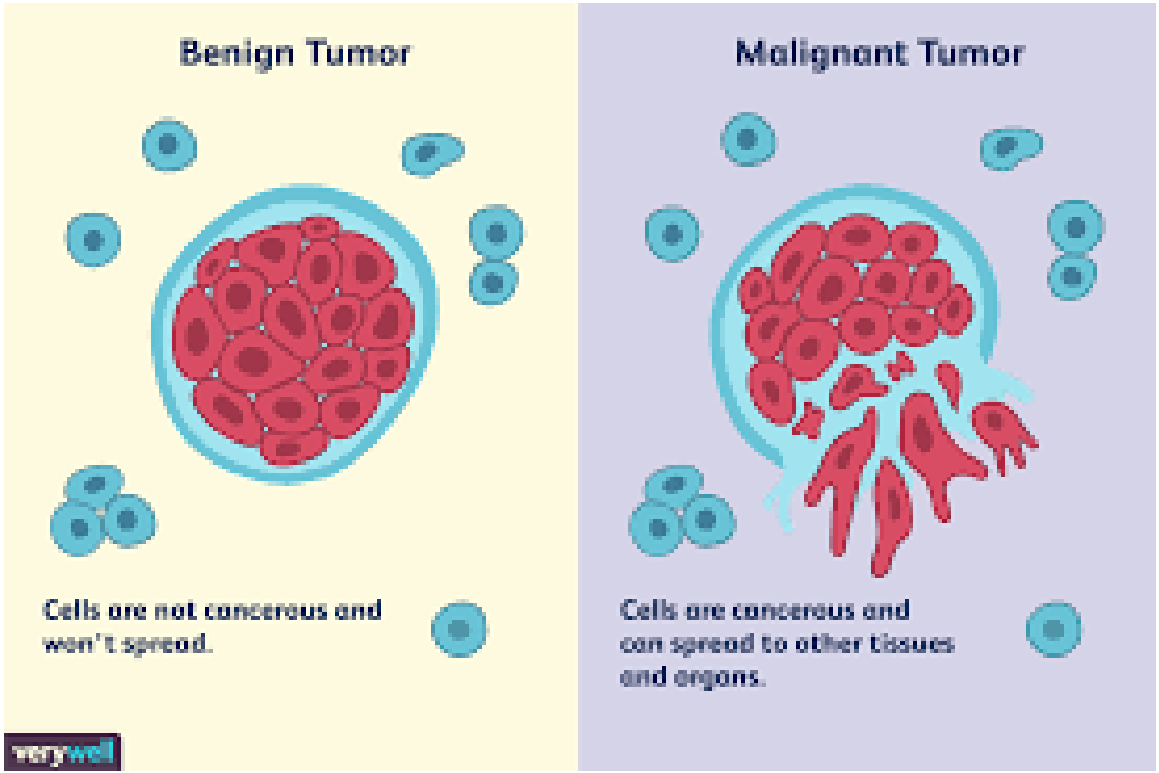
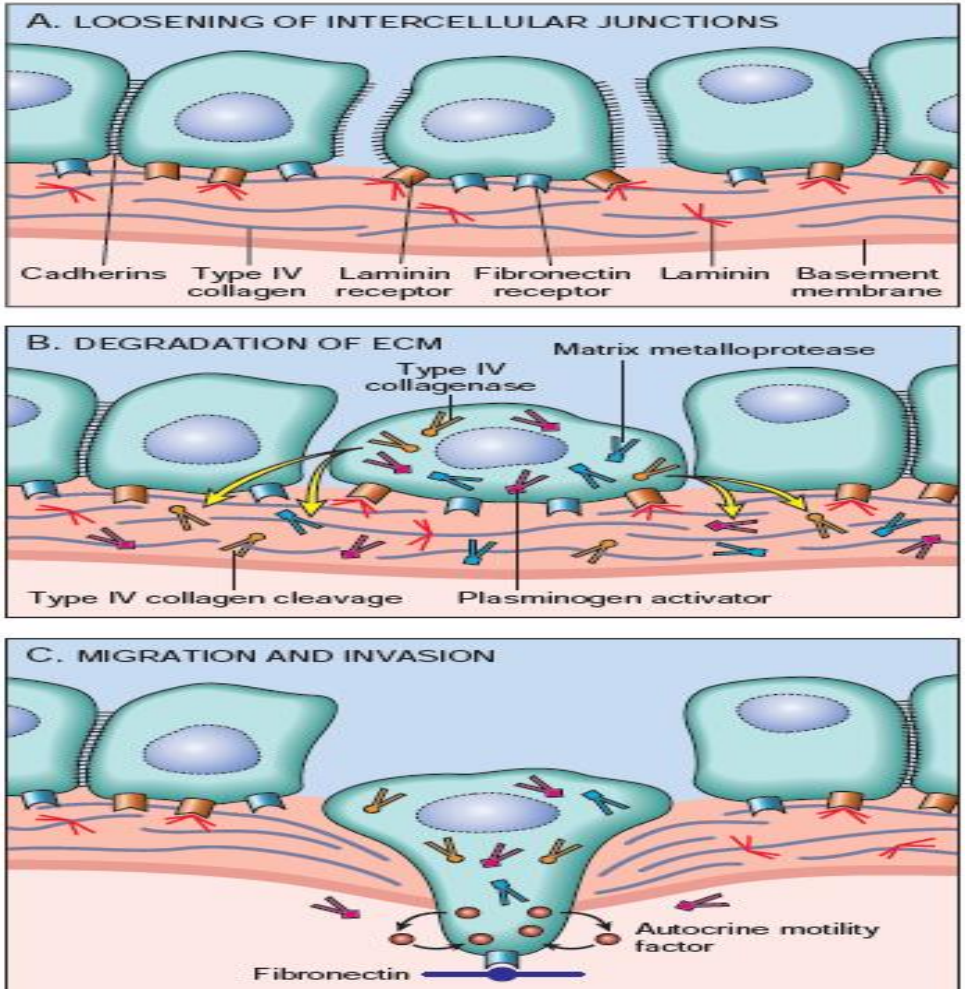

Benign Tumor
Cells are not cancerous and won't spread.
Malignant Tumor
Cells are cancerous and can spread to other tissues and organs.
verywell



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BENIGN TUMOURS

- Encapsulated or circumscribed masses that **expand and push** aside the surrounding normal tissues

- **No invasion and infiltration**

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MALIGNANT TUMOUR

- They are distinguished from benign tumours by **invasion, infiltration** of surrounding tissue
- In general, tumours invade via the **route of least resistance** through tissue spaces, permeate lymphatics, blood vessels,perineural spaces and bone by nutrient foramina.

- **It is the 2nd most reliable sign of malignancy (after metastasis)**

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
2. Clinical features
3. Gross features
4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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METASTASIS (DISTANT SPREAD)

- Spread of tumour by invasion in such a way that **discontinuous secondary tumour mass/masses are formed at the site of lodgement away from primary site**

- Spread of the tumor to other parts because of penetration into blood vessels, lymphatics and the body cavities

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- Benign tumours do not metastasise
- Malignant tumours can metastasise **Excep**

1. **Gliomas of CNS**
2. **Basal cell carcinoma of the skin**

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- **It is the most reliable feature of a malignant tumor**

Routes of Metastasis

- Cancers may spread to distant sites by following pathway

1. Lymphatic spread

2. Haematogenous spread

3. Transcoelomic spread → Spread along body cavities and natural passages (along epithelium lined surfaces, spread via cerebrospinal fluid, implantation).

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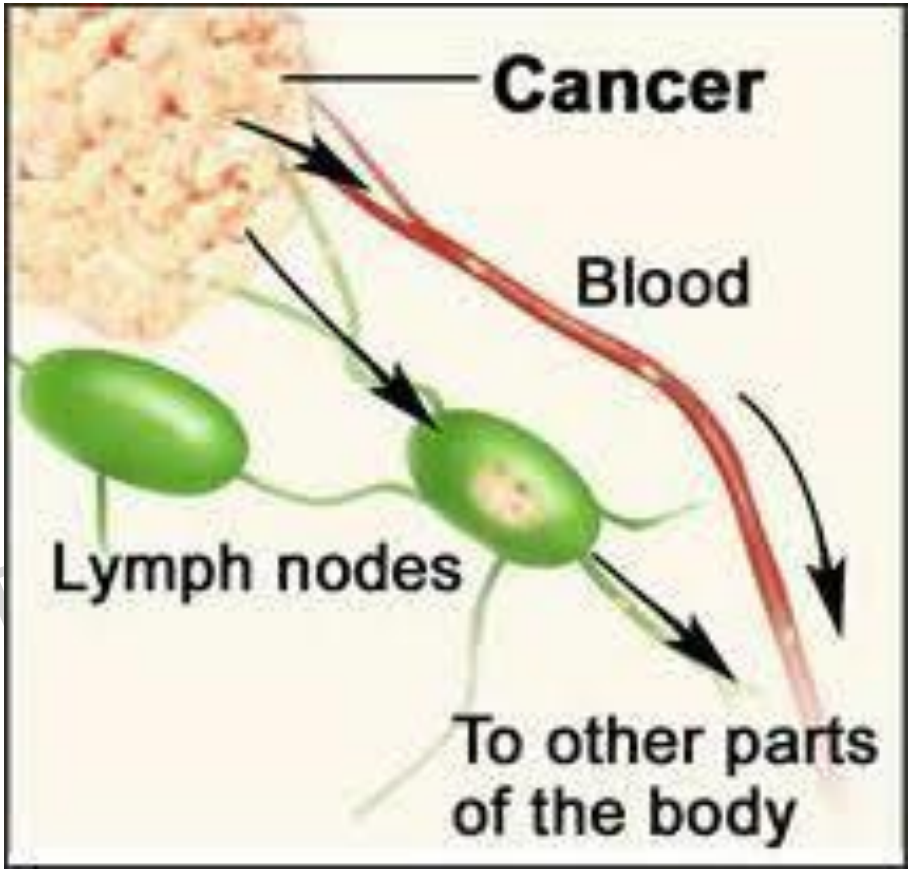
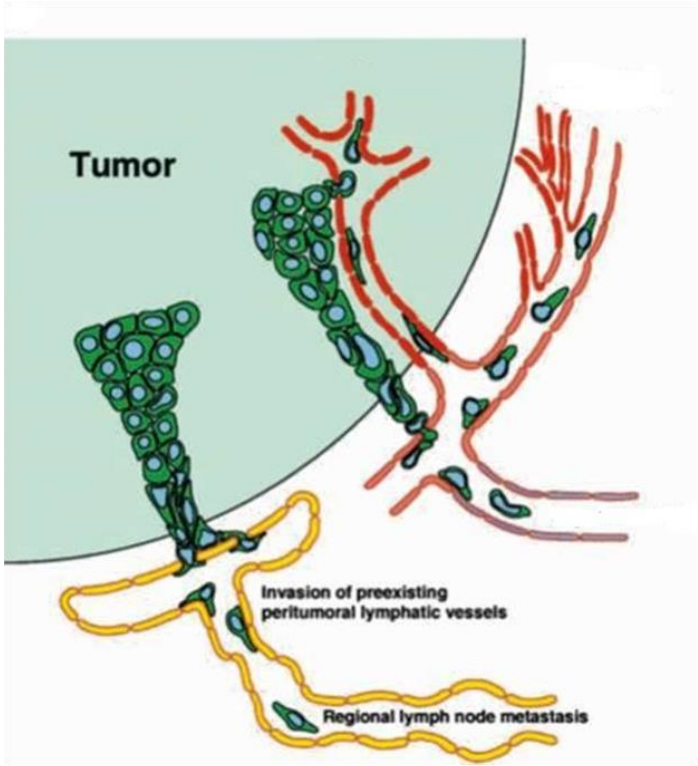
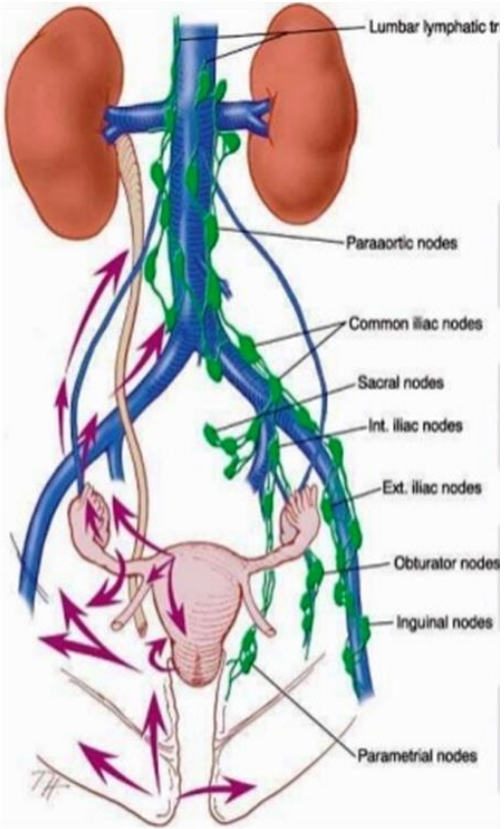
Pathways of spread

Direct seeding of body cavities and surfaces	Lymphatic spread	Hematogenous sprad
• Involvement of peritoneal cavity (in ovarian cancer). • Surface of abdominal viscera (mucus secreting appendicle cancer causing pseudomyxoma peritonei).	• Usual for carcinomas • Pattern of lymph node involvement follows natural route of lymphatic drainage. • **Sentinel lymph node** is the first lymph node to receive lymph flow from a primary tumor. • Seen in melanoma, breast and colon cancer.	• Usual for sarcomas • Thinner walls of veins causes preferential venous invasion in comparison to arteries. • **Liver and lungs** are the most commonly affected organs. • Invasion of veins is particularly prominent is hepatocellular cancer and renal cell cancer.


Cancer
Blood
Lymph nodes
To other parts
of the body





Lymphatic spread of cancer

- **Carcinomas** metastasise by **lymphatic route**

- **Sarcomas** metastasise by **haematogenous route.**

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Routes of Metastasis

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1. LYMPHATIC SPREAD

- Common route for **carcinoma**

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2 forms:

1. **Lymphatic permeation** →The walls of lymphatics are readily invaded by cancer cells and may form a continuous growth in the lymphatic channels

2. **Lymphatic emboli** → the malignant cells may detach to form tumour emboli so as to be carried along the lymph. The tumour emboli are lodged in the subcapsular sinus where they start growing. Later whole lymph node replaced by the metastatic tumour

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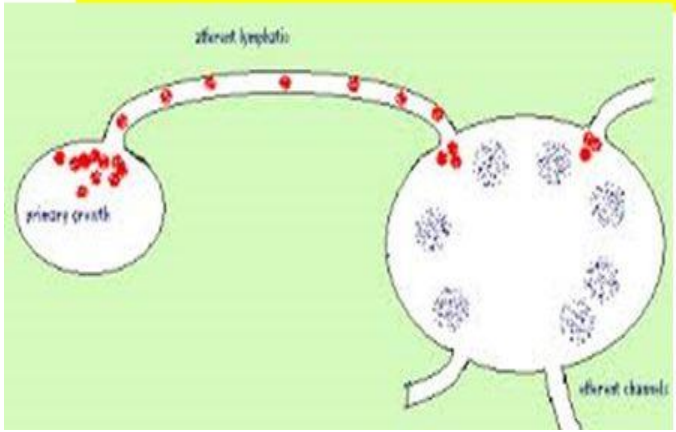
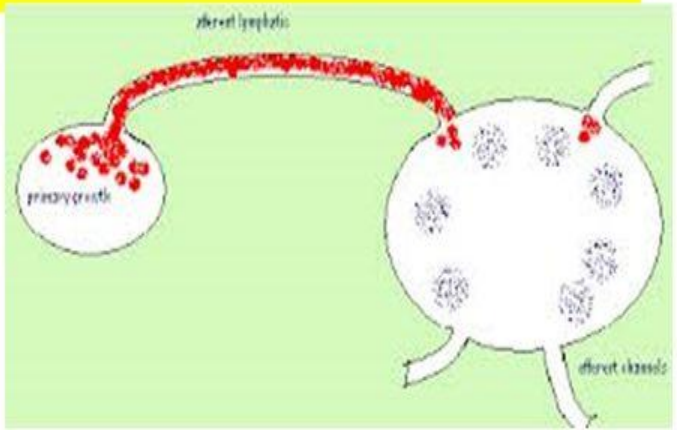
1-Lymphatic spread





Pattern of lymph node involvement

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- 1. The pattern of lymph node involvement follows **the natural routes of lymphatic drainage producing regional nodal metastasis**

- The first node in a regional lymphatics that receives lymph flow from the primary tumor is called **sentinel lymph node.**

- Sentinel lymph node is useful in **breast cancer, vulvar cancer and melanoma.**

- Term 'sentinel lymph node' was first used by **Gould**

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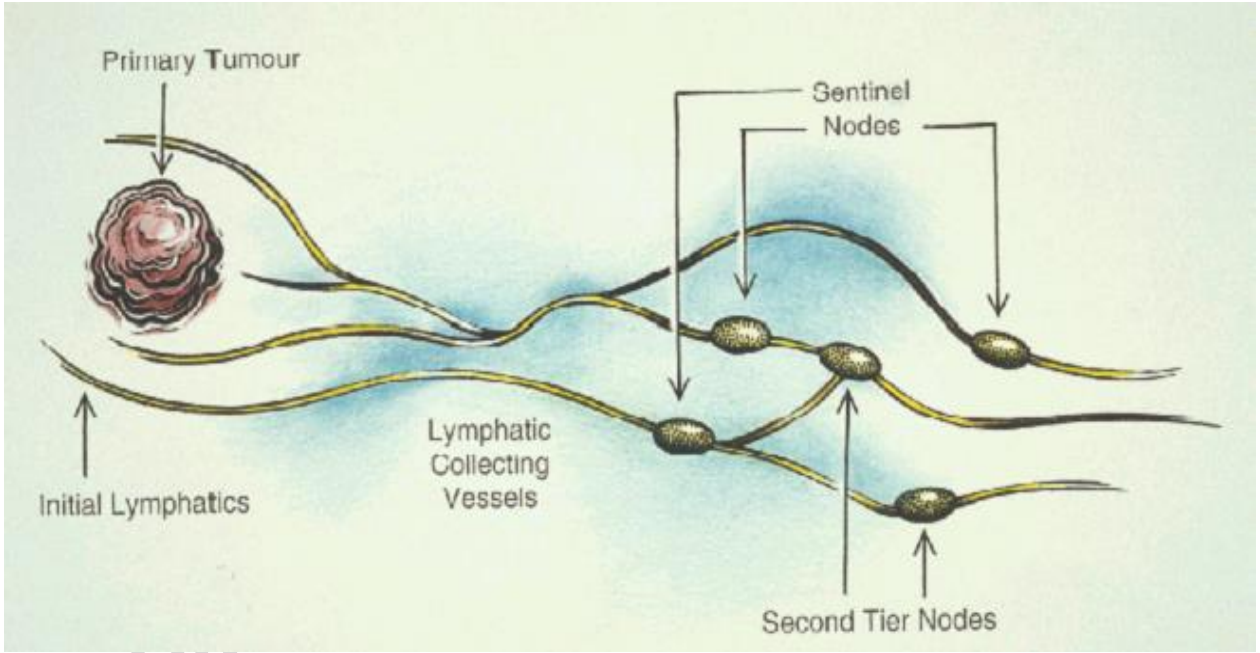

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- 2. Some times local lymph nodes may be bypassed because of venous lymphatic anastomosis → **skip metastasis**

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- 3. Sometimes due to obstruction of the lymphatics by tumour cells, the lymph flow is disturbed and tumour cells spread against the flow of lymph causing **retrograde metastases**

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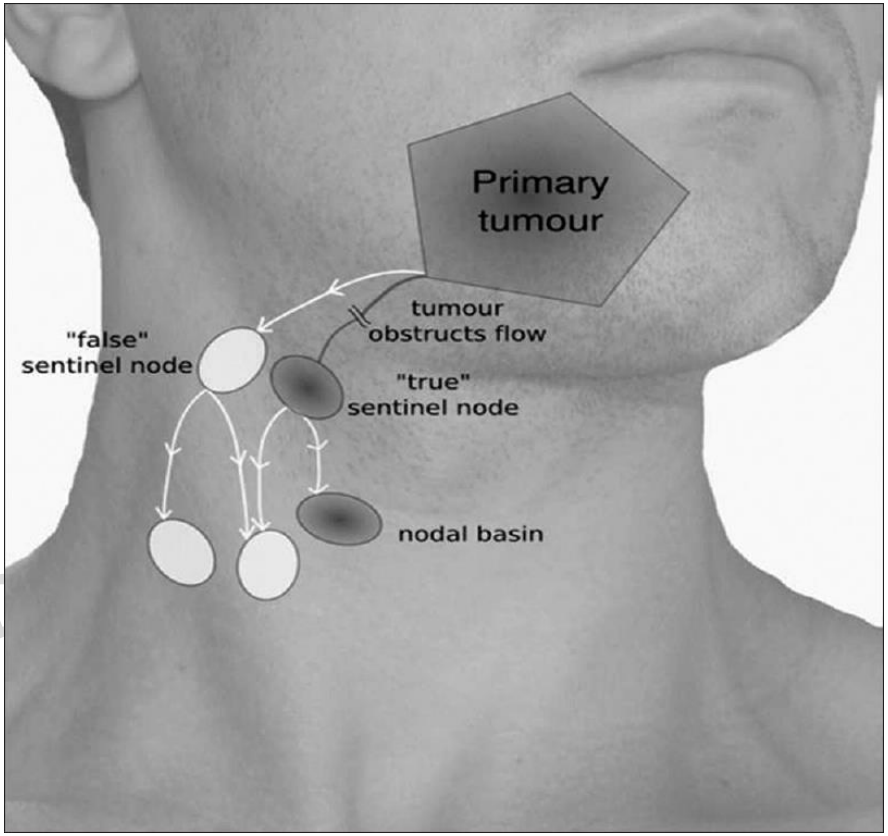

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- In the lymph node tumor cells lodge in first in **subcapsular sinus**

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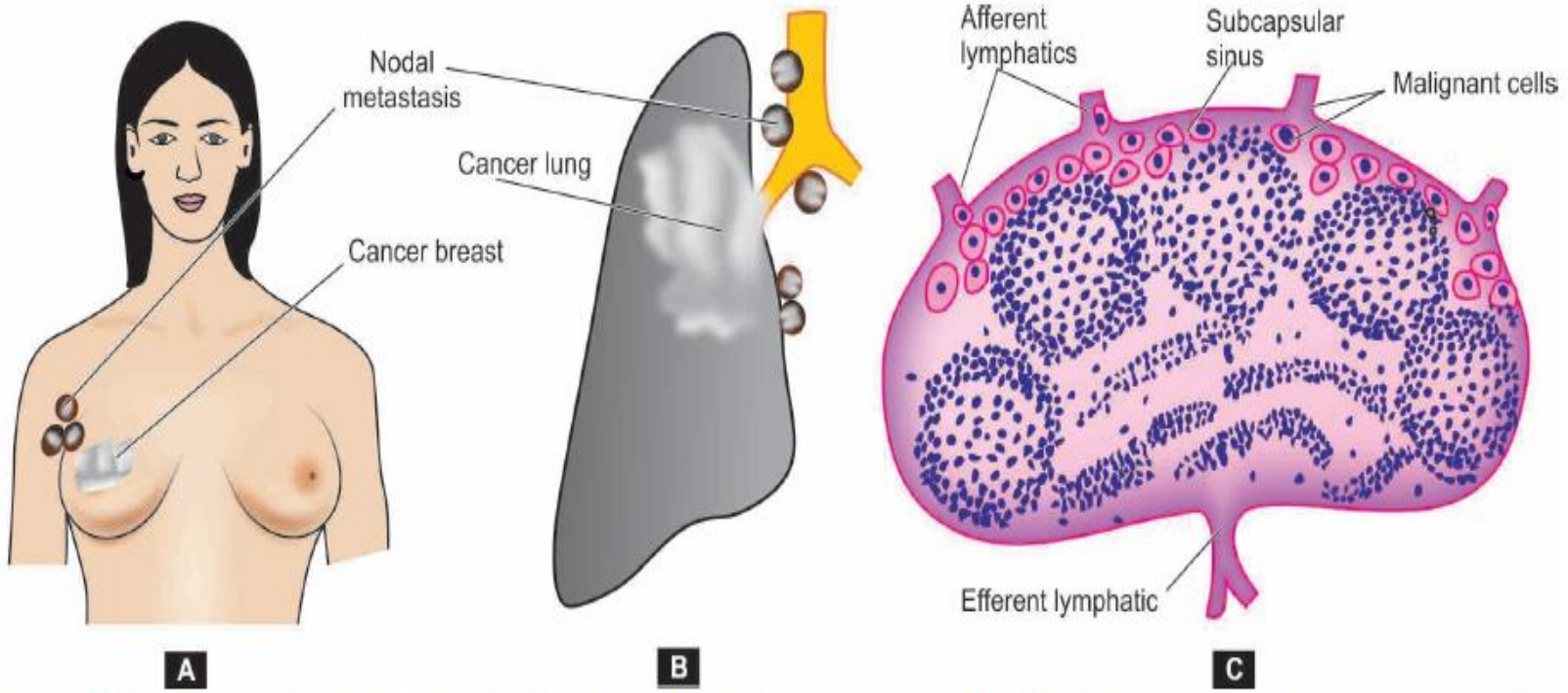

Figure 7.11 Regional nodal metastasis. A, Axillary nodes involved by carcinoma breast. B, Hilar and para-tracheal lymph nodes involved by bronchogenic carcinoma. C, Lymphatic spread begins by lodgement of tumour cells in subcapsular sinus via afferent lymphatics entering at the convex surface of the lymph node

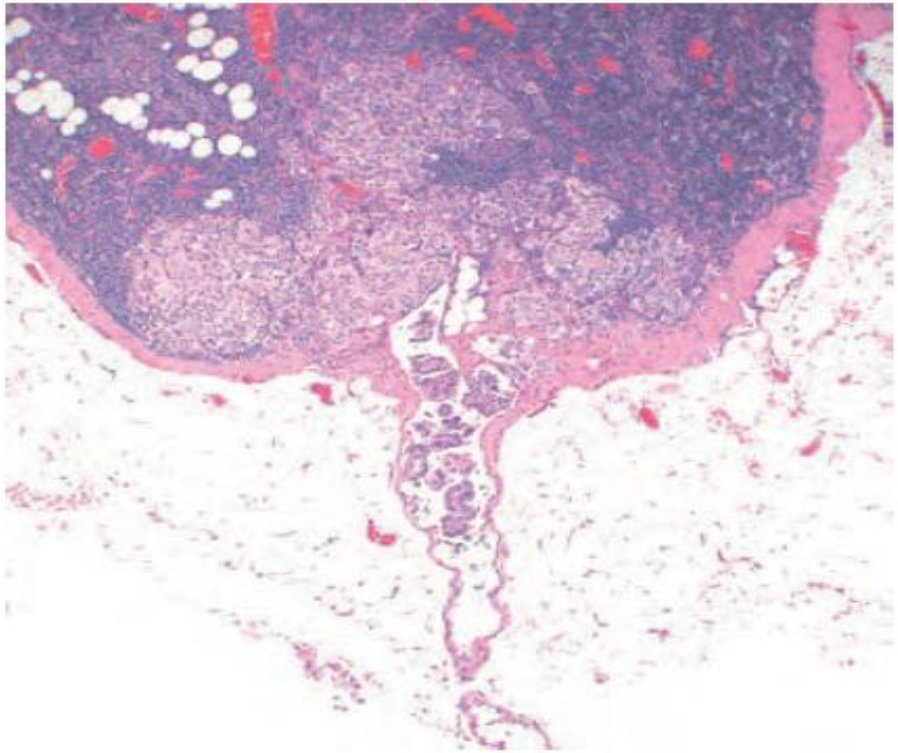

Figure 7-16 Axillary lymph node with metastatic breast carcinoma. Note the aggregates of tumor cells within the substance of the node and the dilated lymphatic channel. (Courtesy Dr. Susan Lester, Brigham and Women's Hospital, Boston, Mass.)

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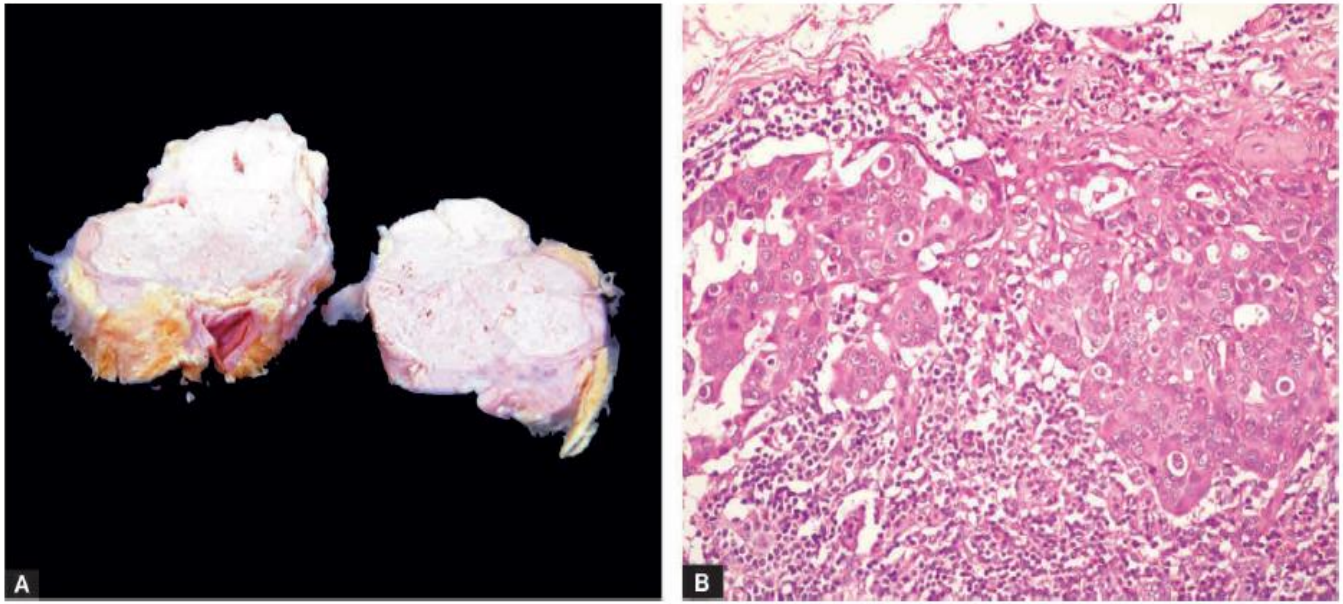

Figure 7.12 Metastatic carcinoma in lymph nodes. A, Matted mass of lymph nodes is surrounded by increased fat. Sectioned surface shows merging capsules of lymph nodes and replacement of grey brown tissue of nodes by large grey white areas of tumour. B, Masses of malignant cells are seen in the subcapsular sinus and extending into the underlying nodal tissue.

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REMEMBER

- **Virchow's lymph node** is nodal metastasis to supraclavicular lymph node from cancers of abdominal organs e.g. cancer stomach, colon, and gallbladder.

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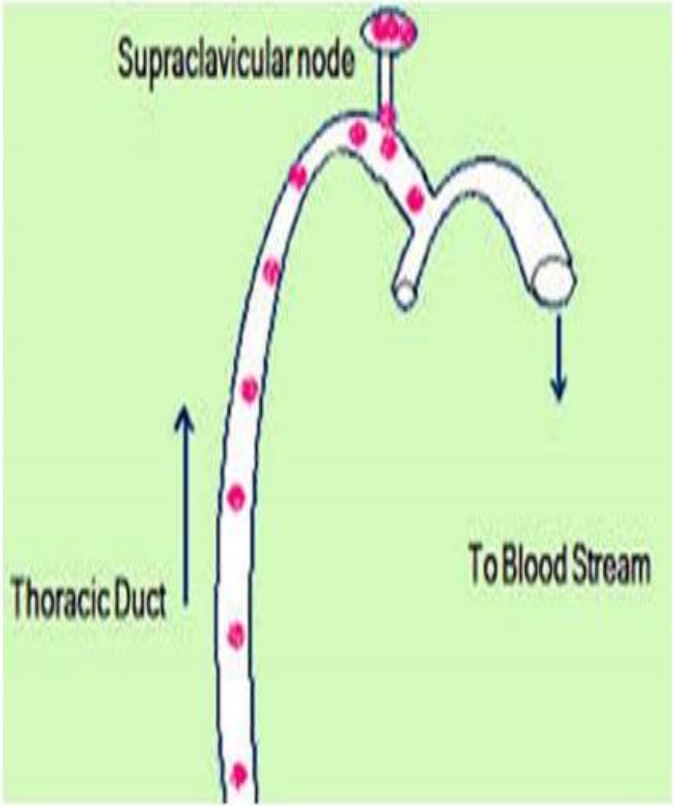
Supraclavicular node
Thoracic Duct
To Blood Stream

Routes of Metastasis

- Cancers may spread to distant sites by following pathway

1. Lymphatic spread

2. Haematogenous spread

3. Transcoelomic spread → Spread along body cavities and natural passages (along epithelium lined surfaces, spread via cerebrospinal fluid, implantation).

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2. HAEMATOGENOUS SPREAD

- common route for **sarcomas**

- Sites commonly occurs are: the liver, lungs, brain, bones, kidney and adrenals, all of which provide ‘good soil’ for the growth of ‘good seeds’, i.e. **seed-soil theory**

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- **Veins** are more commonly involved than arteries because veins have thinner walls that can be penetrated readily
- In contrast arteries have thicker walls.

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1. With **venous invasion**, the tumor cells in blood follow the venous flow draining the site of neoplasm.

- So **liver and lung** are the most frequent organs involved in hematogenous spread because

1. **All portal area drainage flows to the liver**
2. **All caval blood flows to the lung**

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2. Arterial spread may occur when tumor cells pass through the pulmonary capillary beds or pulmonary A-V shunts or when pulmonary metastasis give rise to additional tumor emboli.

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3. Retrograde spread by blood route may occur at unusual sites due to retrograde spread after venous obstruction.

- eg vertebral metastases in cancers of the thyroid and prostate.

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REMEMBER

- Most common site of metastasis is **LIVER** followed by **LUNG** as 2nd most common site

- All cancers malignant tumors metastatize except **glioma and rodent ulcer (basal cell carcinoma)**

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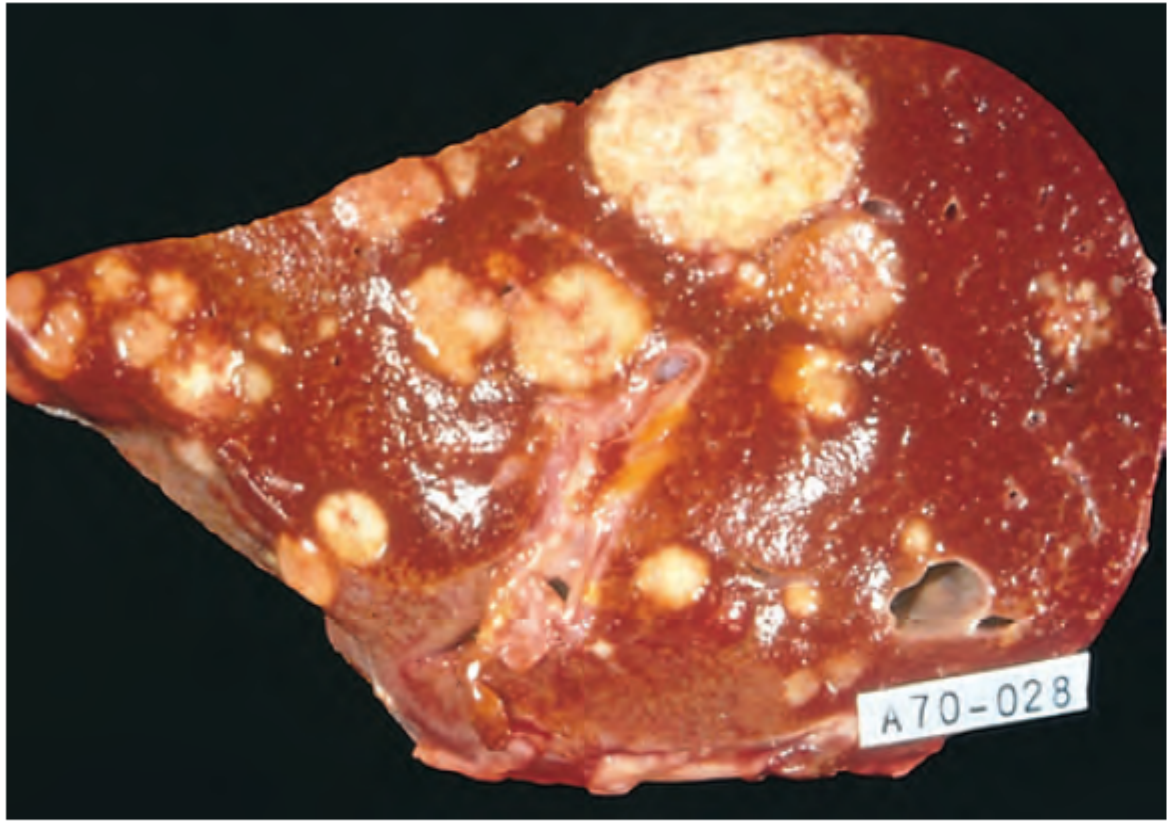

Figure 7-17 A liver studded with metastatic cancer.

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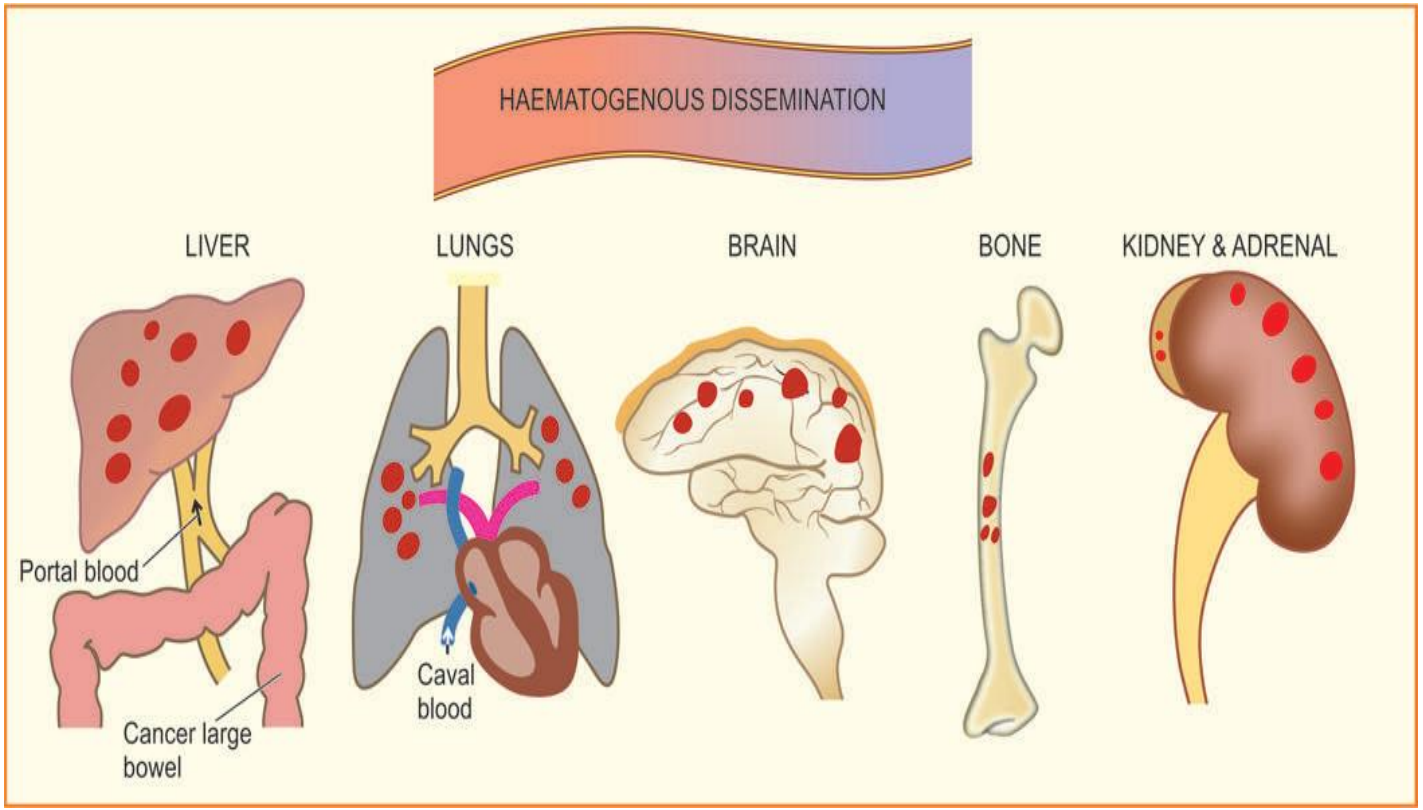
HAEMATOGENOUS DISSEMINATION
LIVER
LUNGS
BRAIN
BONE
KIDNEY & ADRENAL
Portal blood
Cancer large bowel
Caval blood

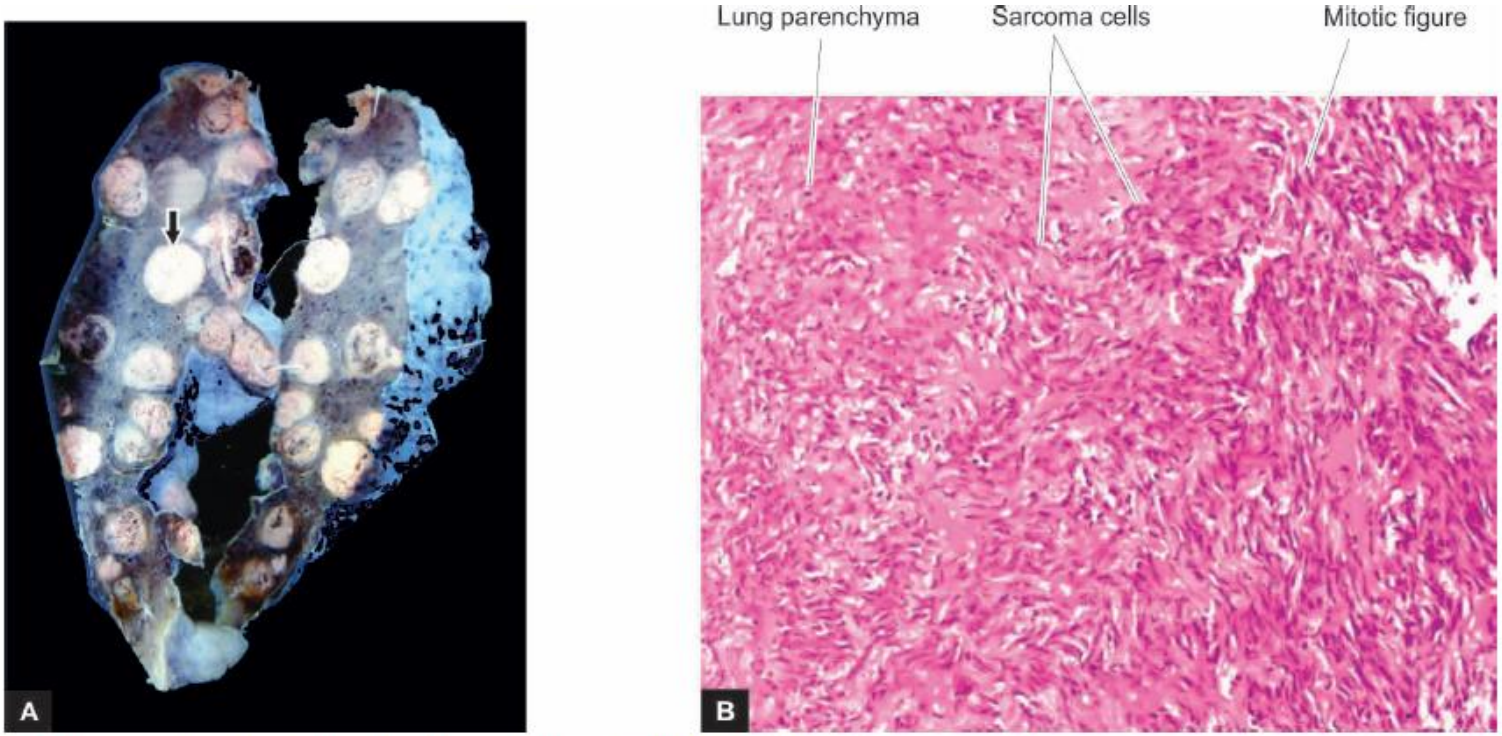

Figure 7.14 Metastatic sarcoma lung. A, Sectioned surface of the lung shows replacement of slaty-grey spongy parenchyma with multiple, firm, grey-white nodular masses, some having areas of haemorrhages and necrosis. B, Microscopic appearance of pulmonary metastatic deposits from sarcoma.

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Routes of Metastasis

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3. Transcoelomic spread → Spread along body cavities and natural passages (along epithelium lined surfaces, spread via cerebrospinal fluid, implantation).

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3. Transcoelomic spread

(i) Direct seeding into body cavities or surface

(ii) Spread via cerebrospinal fluid

(iii) Implantation

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(i) Direct seeding into body cavities or surface

- It occurs when a malignant neoplasm penetrates into a **natural open field**
- Tumour clusters of tumour cells break off to be carried in the coelomic fluid and are implanted elsewhere in the body cavity
- Most common cavity involved is **peritoneal cavity,** but other cavities may also be involved, e.g., pleural, pericardial, joint space, subarachnoid.

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- Eg.

a) Carcinoma of the stomach seeding to both ovaries **(Krukenberg tumour)**

b) Carcinoma of the ovary spreading to the entire peritoneal cavity

c) Pseudomyxoma peritonei is the gelatinous coating of the peritoneum from mucin-secreting carcinoma of the ovary or apppendix.

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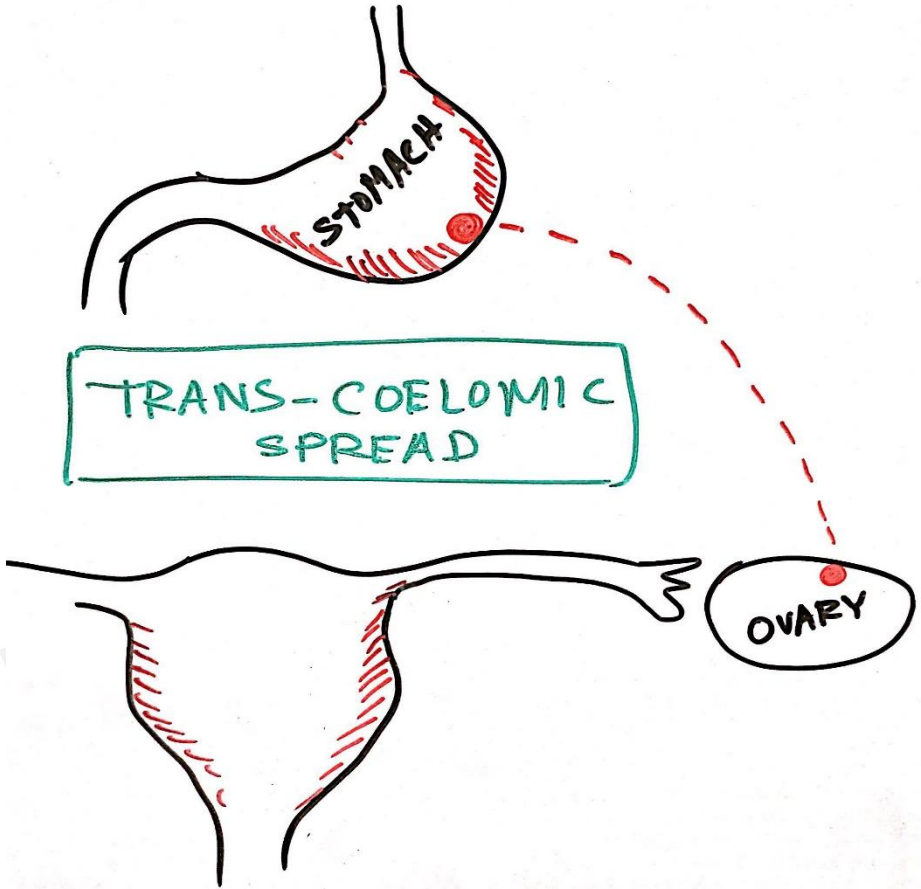

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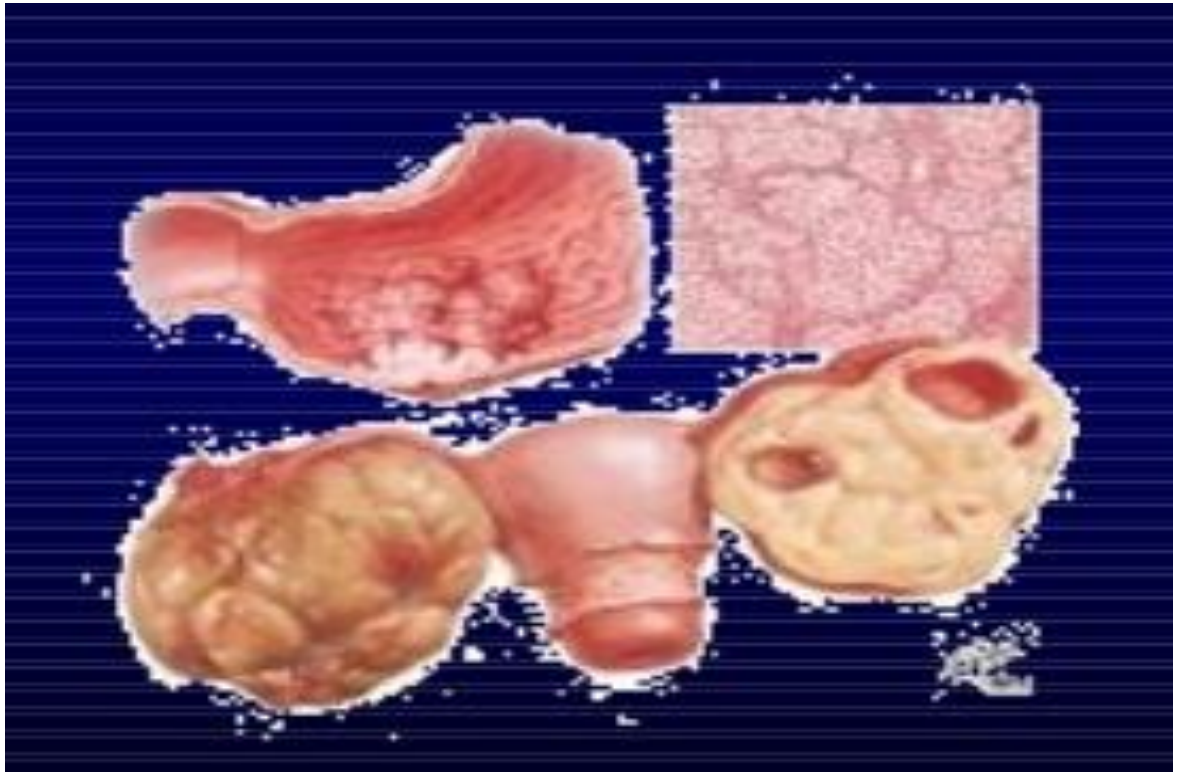

ii) Spread via cerebrospinal fluid

- Malignant tumour of the **ependyma and leptomeninges** may spread by release of tumour fragments and tumour cells into the CSF and produce metastases at other sites in the central nervous system.

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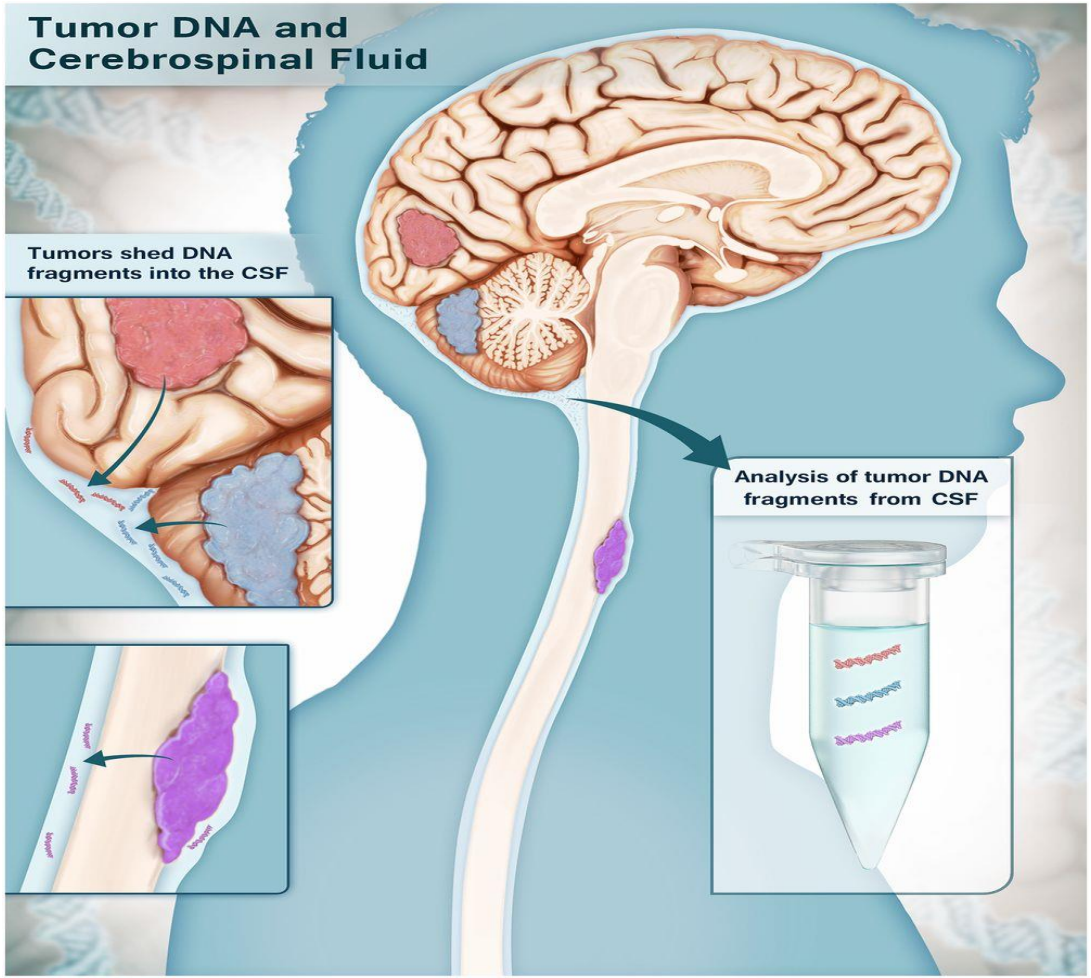

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iii) Implantation

- spread of some cancers by implantation by surgeon's scalpel, needles, sutures, and direct prolonged contact of cancer of the lower lip causing its implantation to the apposing upper lip.

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MECHANISM AND BIOLOGY OF INVASION AND METASTASIS

8 steps

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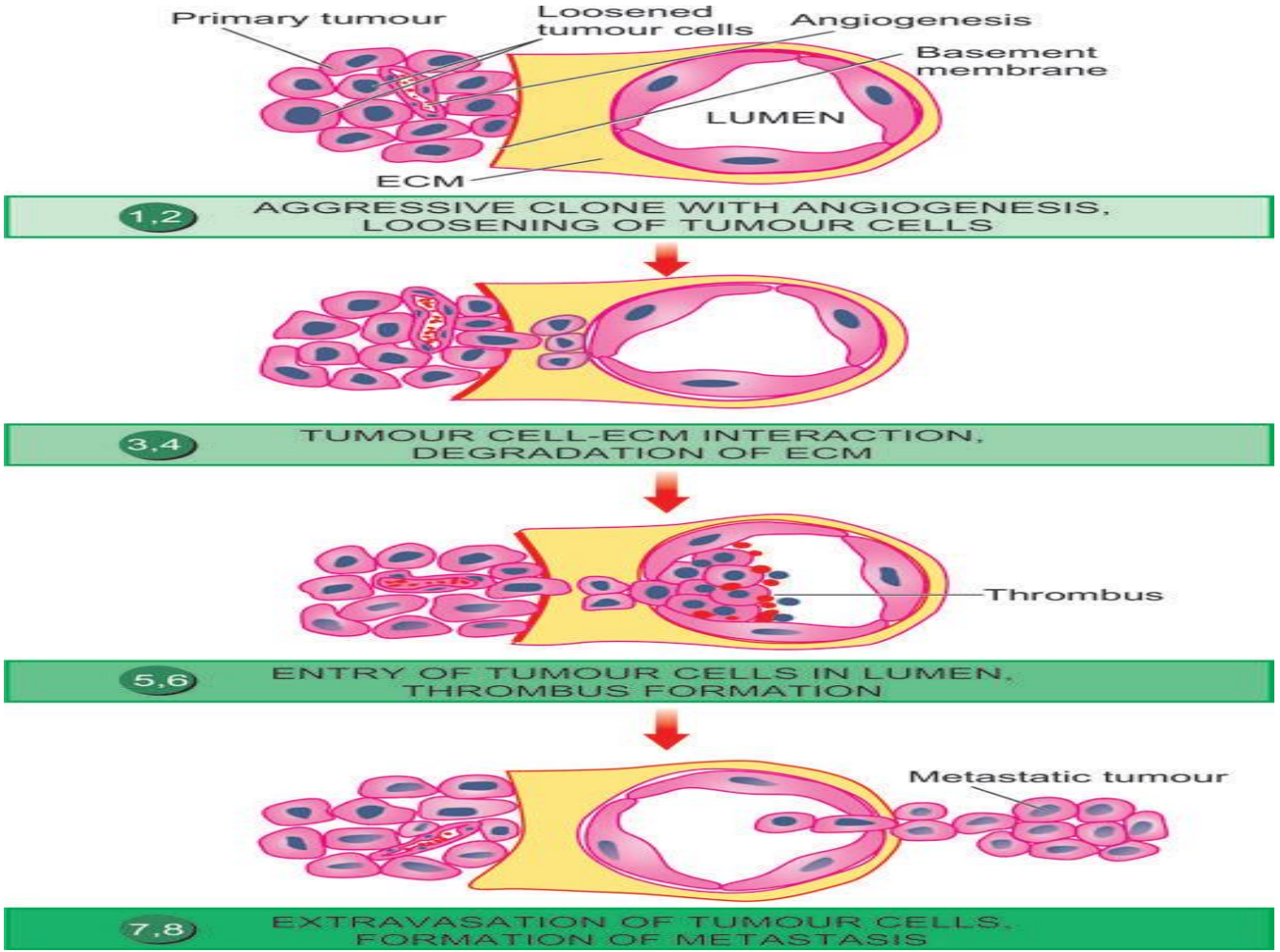
Primary tumour
Loosened tumour cells
Angiogenesis
Basement membrane
LUMEN
ECM
1,2
AGGRESSIVE CLONE WITH ANGIOGENESIS, LOOSENING OF TUMOUR CELLS
3,4
TUMOUR CELL-ECM INTERACTION, DEGRADATION OF ECM
Thrombus
5,6
ENTRY OF TUMOUR CELLS IN LUMEN, THROMBUS FORMATION
Metastatic tumour
7,8
EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

1. Clonal proliferation and angiogenesis→

- Development of rapidly proliferating clone of cancer cells

- **Tumour heterogeneity**, i.e. in the population of monoclonal tumour cells, a subpopulation or clone of tumour cells is involved in the development of metastasis.

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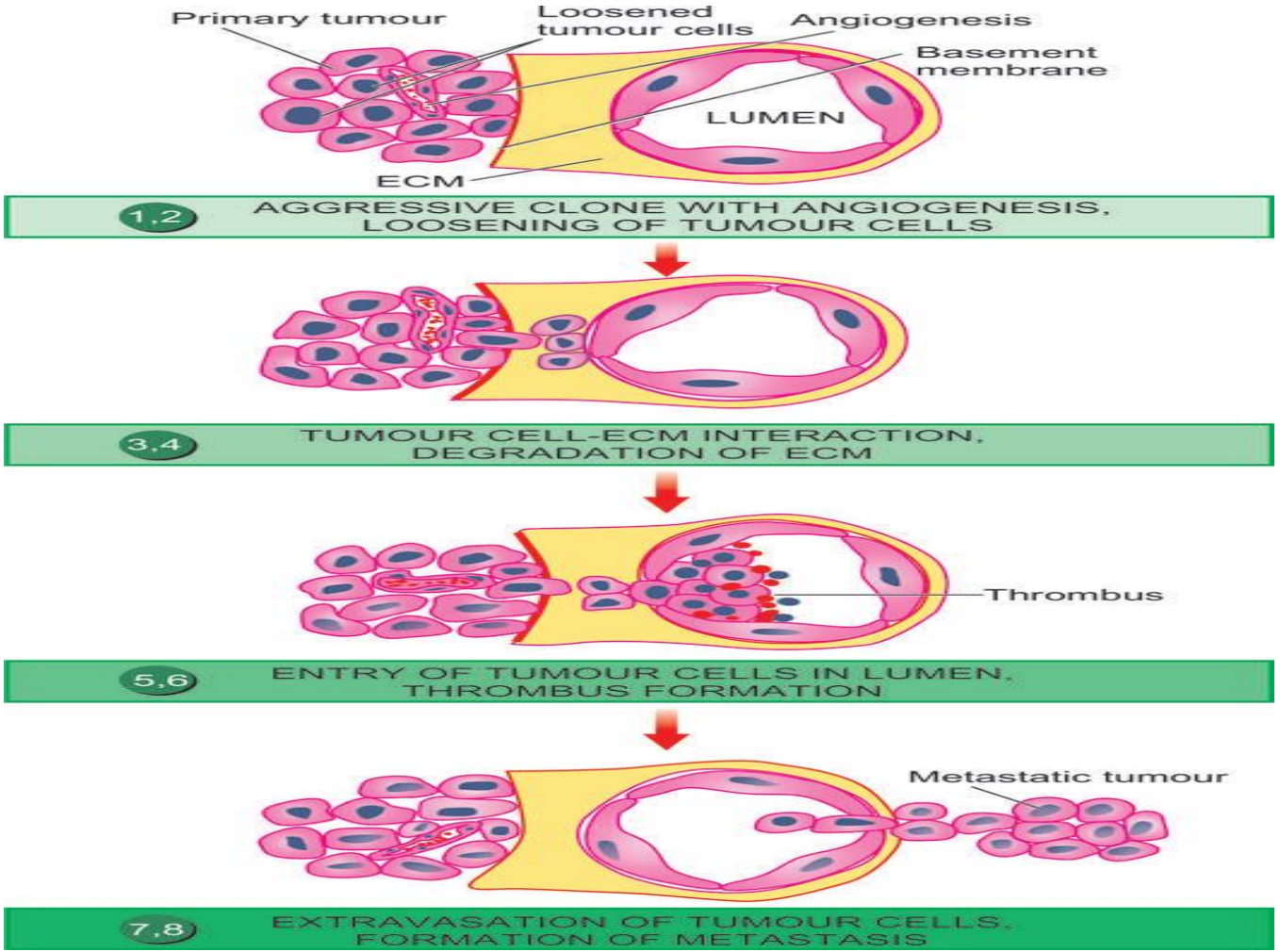
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EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

2. Tumour cell loosening

- Normal cells remain glued to each other due to presence of cell adhesion molecules (CAMs) i.e. E (epithelial)-cadherin.

- In cancers, there is either **loss or inactivation of E-cadherin and CAMs** results in loosening of cancer cells.

- **Mutation in gene encoding for E-cadherin (CDH-1) is associated with gastric carcinoma**

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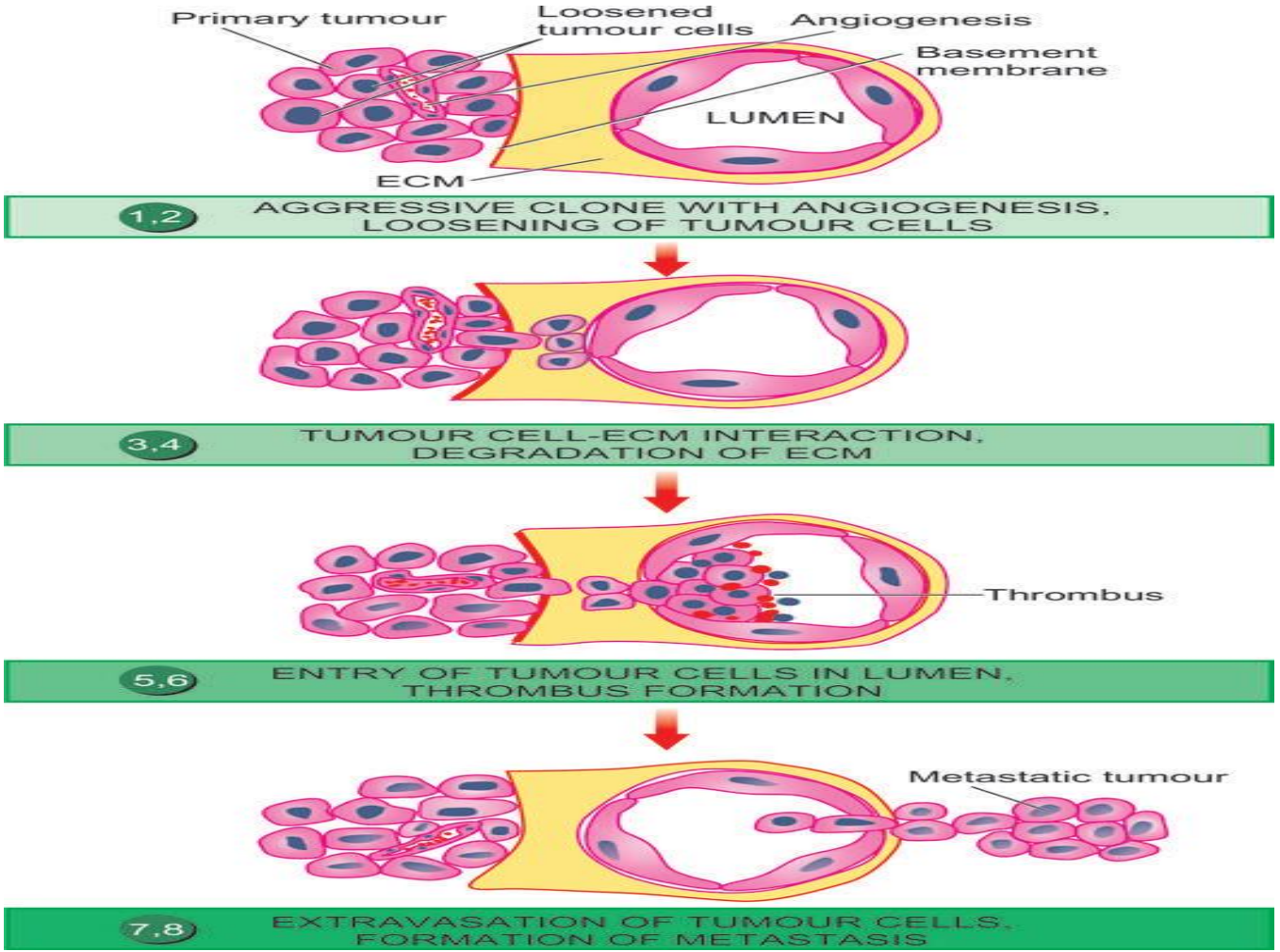
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3. Tumour cell-ECM interaction

- Loosened cancer cells are now attached to ECM proteins, mainly **laminin,fibronectin,vitronectin, and collagen.**
- This attachment is facilitated due to profoundness of **receptors** on the cancer cells for both these proteins.
- There is also loss of integrins, the transmembrane receptors, further favouring invasion.

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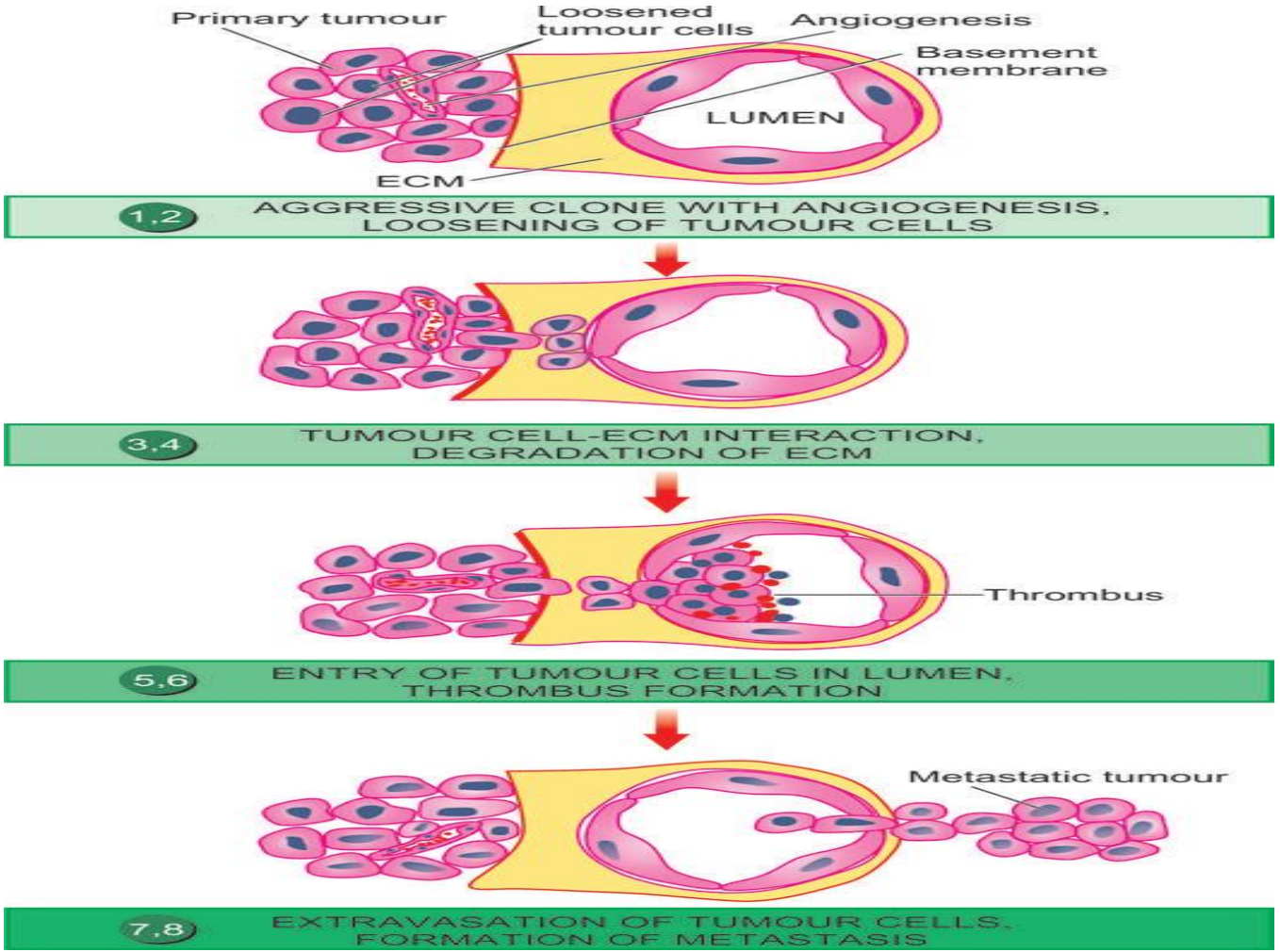
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4. Degradation of ECM

- Tumour cells overexpress proteases and matrix-degrading enzymes, metalloproteinases (e.g. collagenases and gelatinase)
- the inhibitors of metalloproteinases are decreased

- These enzymes bring about dissolution of ECM—

1. firstly basement membrane of tumour itself,
2. then make way for tumour cells through the interstitial matrix
3. finally dissolve the basement membrane of the vessel wall

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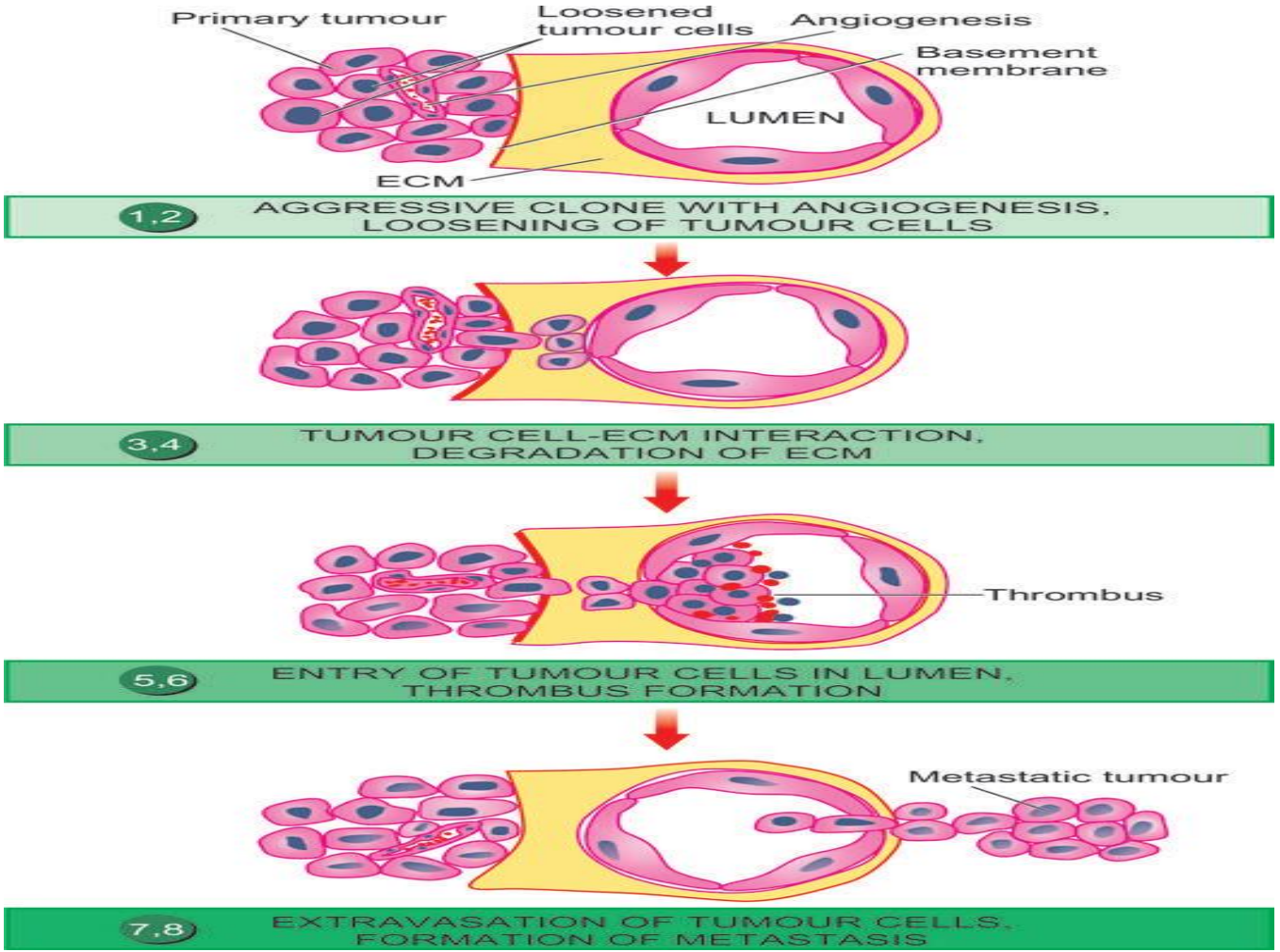
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5. Entry of tumour cells into capillary lumen

- **Autocrine motility factor (AMF)**, a cytokine derived from tumour cells which stimulates receptor-mediated motility of tumour cells.

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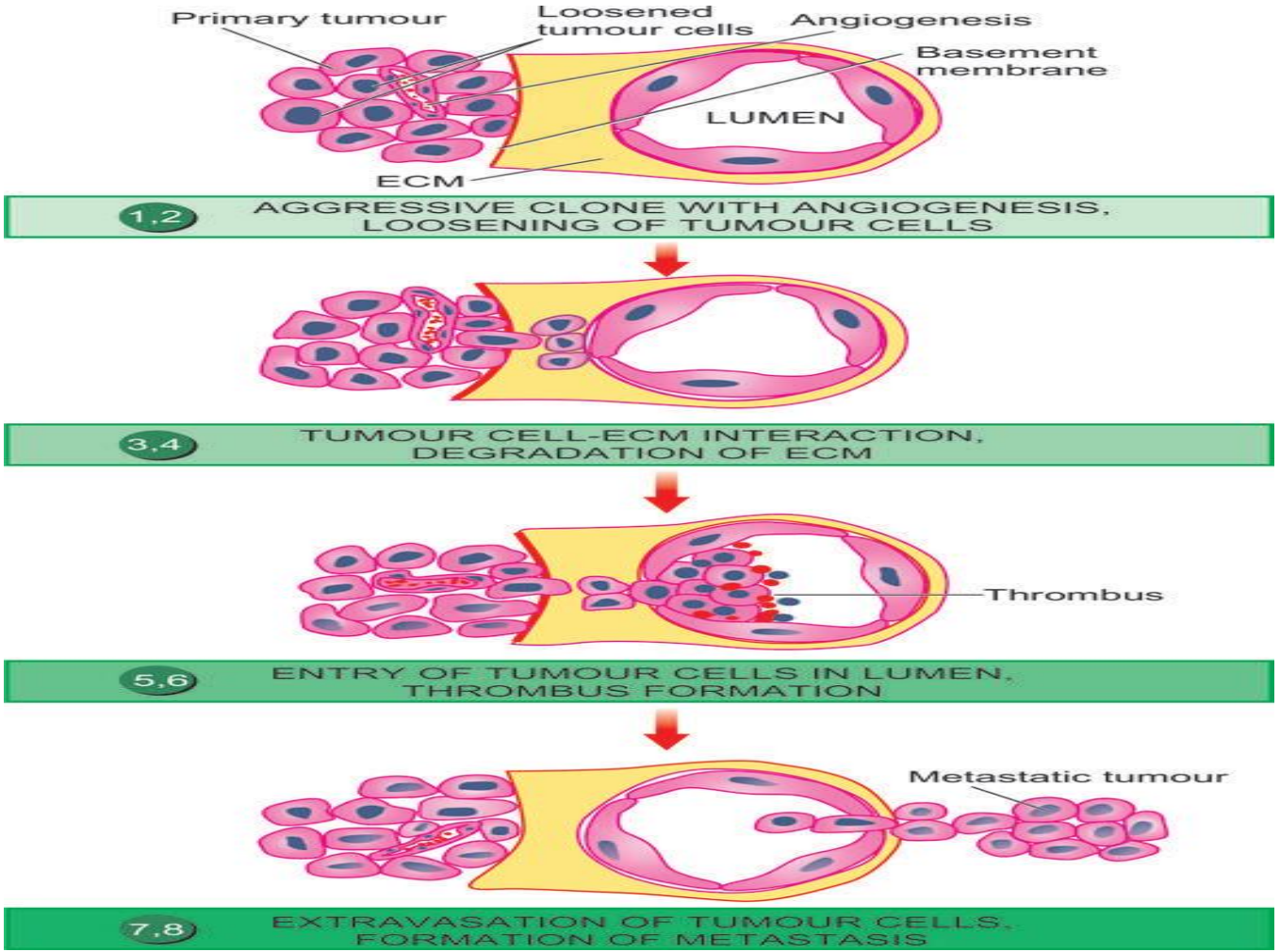
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EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

6. Thrombus formation

- The tumour cells are now covered with constituents of the circulating blood and form the thrombus

- Thrombus **provides nourishment to the tumour cells and also protects them from the immune attack by the circulating host cells**

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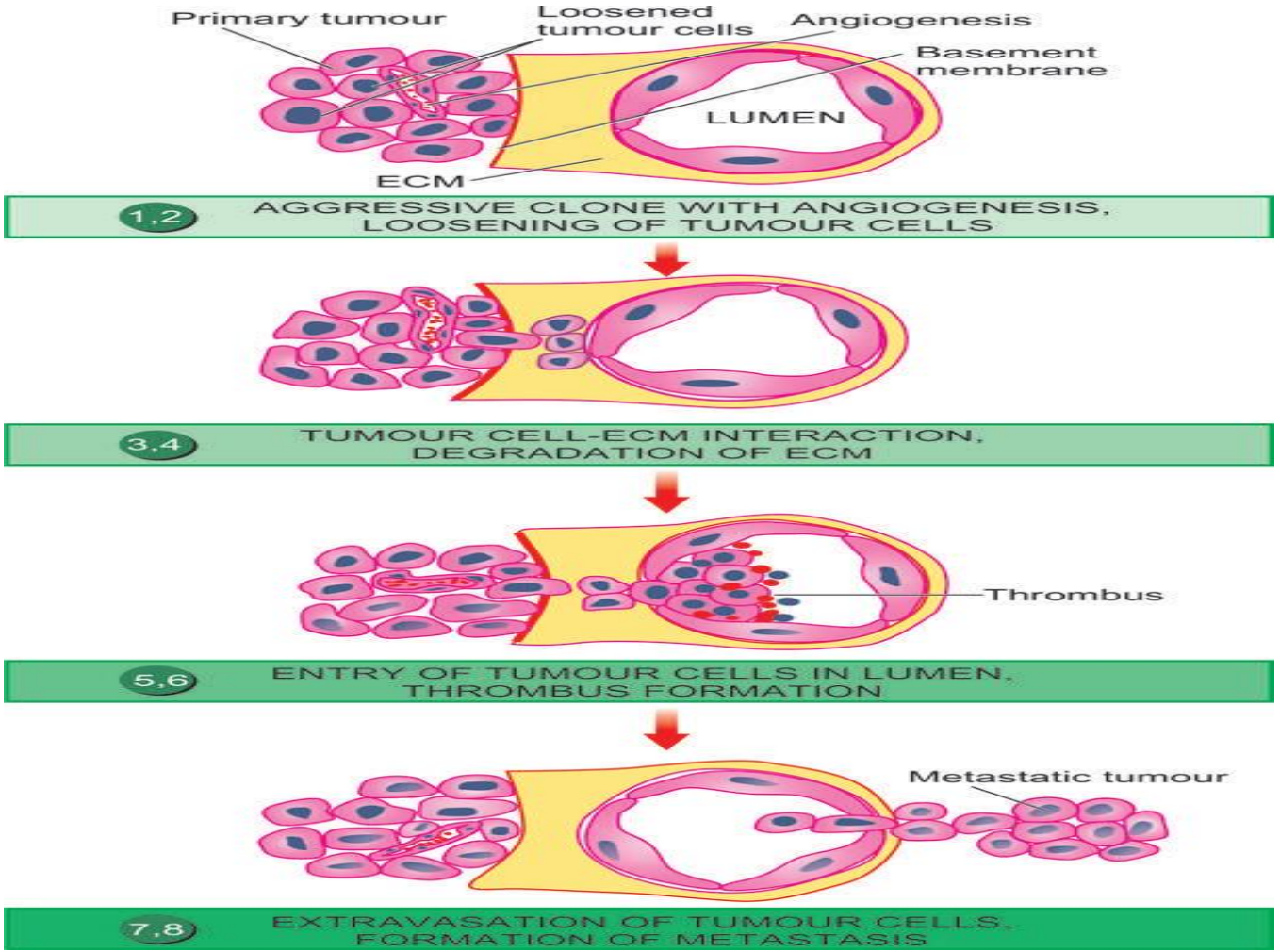
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7,8
EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

7. Extravasation of tumour cells

- Tumour cells attach to vascular endothelium
- Extravasate to the extravascular space.

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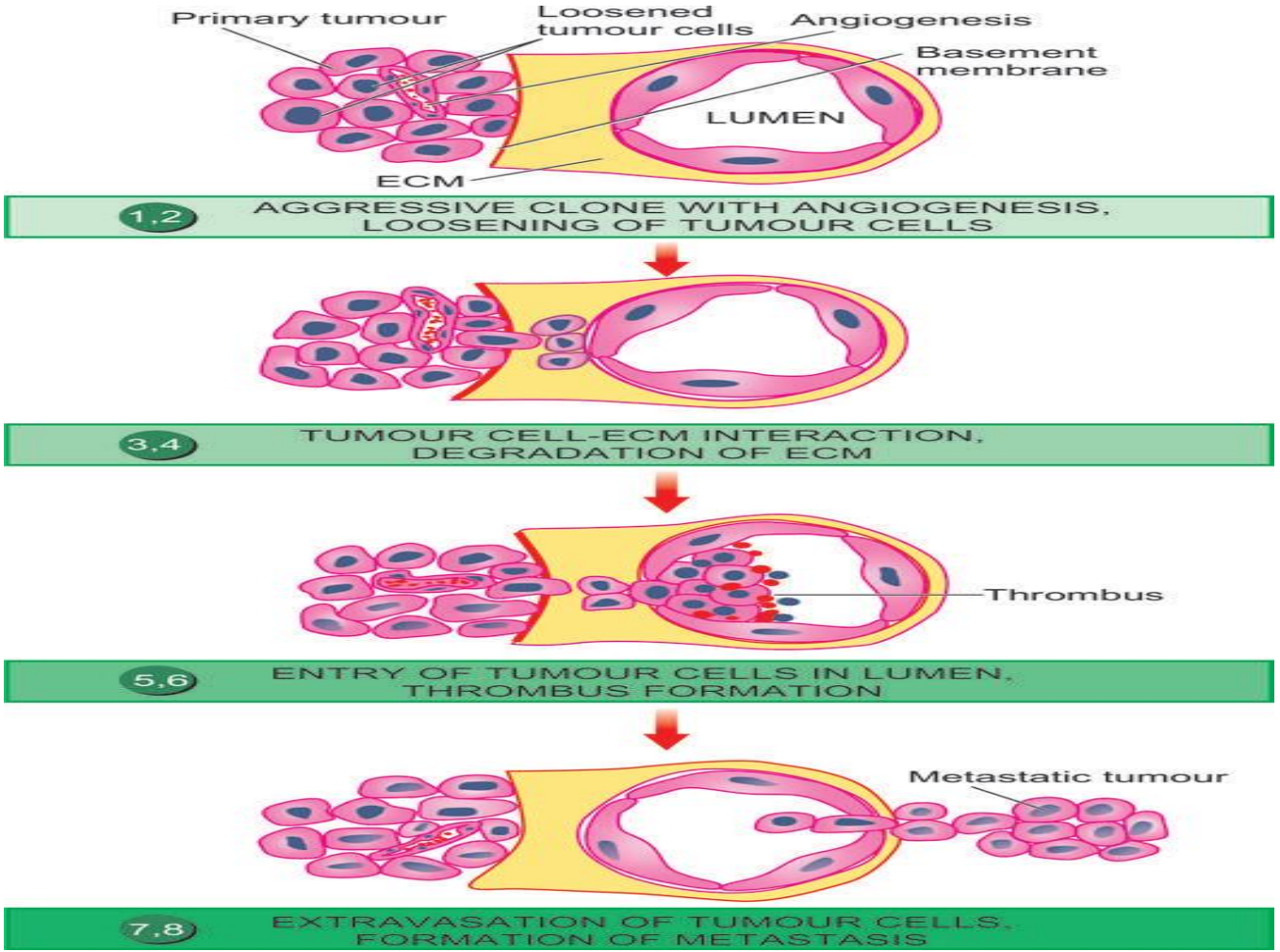
Primary tumour
Loosened tumour cells
Angiogenesis
Basement membrane
LUMEN
ECM
1,2
AGGRESSIVE CLONE WITH ANGIOGENESIS, LOOSENING OF TUMOUR CELLS
3,4
TUMOUR CELL-ECM INTERACTION, DEGRADATION OF ECM
Thrombus
5,6
ENTRY OF TUMOUR CELLS IN LUMEN, THROMBUS FORMATION
Metastatic tumour
7,8
EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

8. Survival and growth of metastatic deposit

- The extravasated malignant cells on lodgement in the right environment

- Grow further under the influence of **growth factors** produced tumour Some of the growth promoting factors

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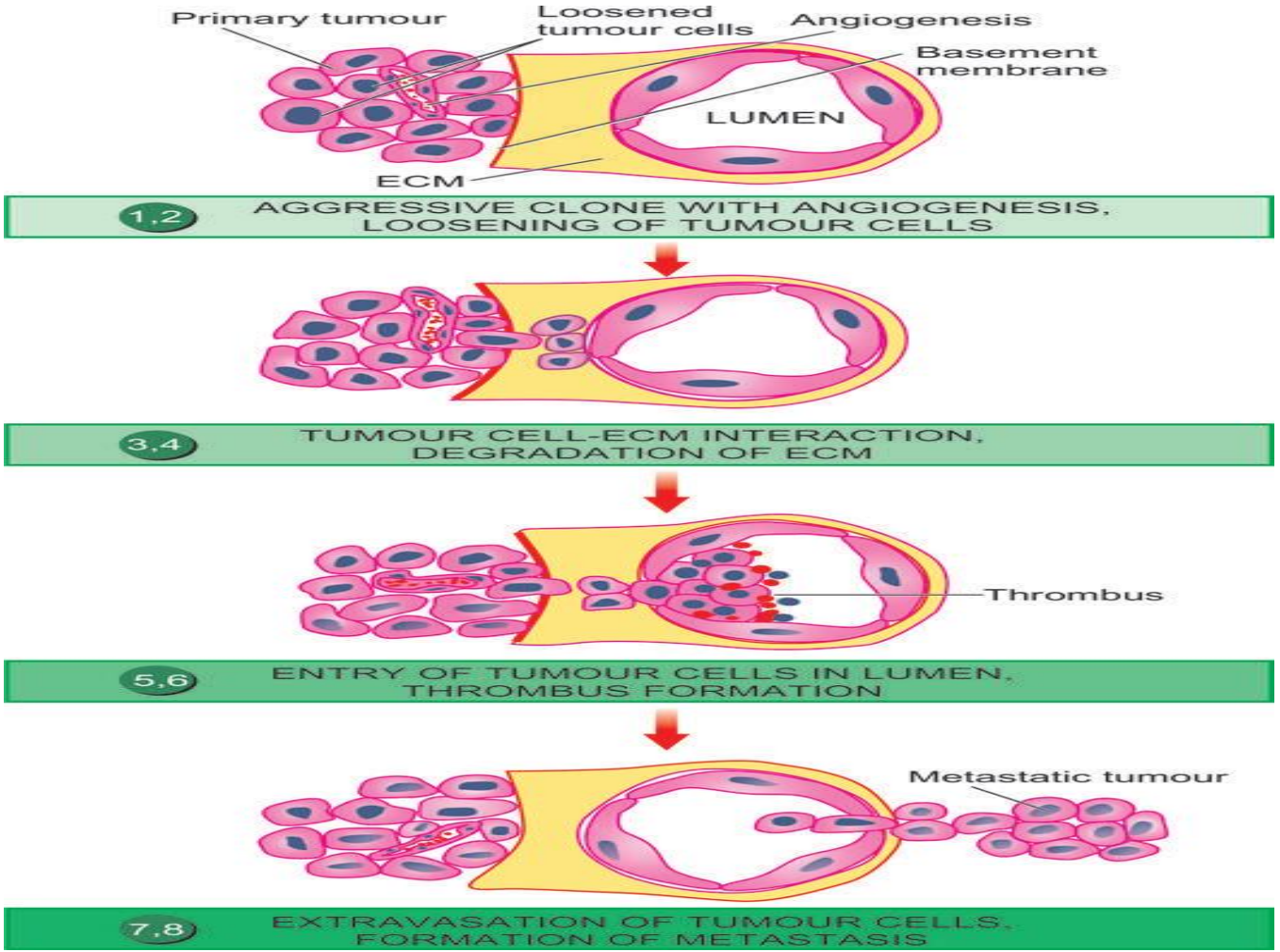
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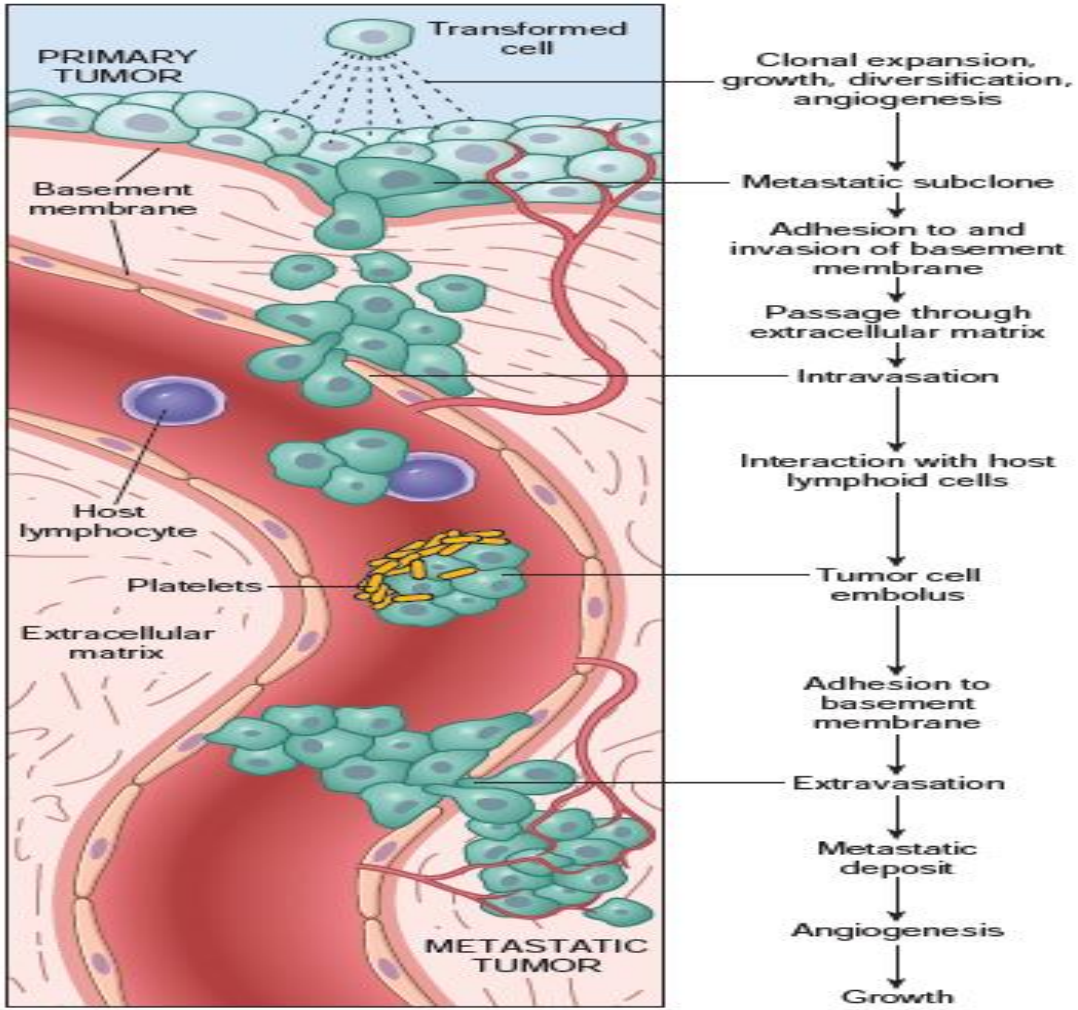
PRIMARY TUMOR
Transformed cell
Clonal expansion, growth, diversification, angiogenesis
Basement membrane
Metastatic subclone
Adhesion to and invasion of basement membrane
Passage through extracellular matrix
Intravasation
Interaction with host lymphoid cells
Host lymphocyte
Platelets
Tumor cell embolus
Extracellular matrix
Adhesion to basement membrane
Extravasation
Metastatic deposit
Angiogenesis
Growth
METASTATIC TUMOR

REMEMBER

- **Metastatis gene** → **Ezrin** is the only metastatis gene, that has been identified till now. It is necessary for metastasis of rhabdomyosarcoma and osteosarcoma.

- **Antimetastatis gene** → **NM 23, KAI-1,Kiss gene.**

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CHARACTERISTICS OF TUMOURS

1. Rate of growth
2. Clinical features
3. Gross features
4. Microscopic features
5. Spread of tumours
    a. Local invasion or direct spread
    b. Metastasis or distant spread

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	FEATURE	BENIGN	MALIGNANT
I.	CLINICAL AND GROSS FEATURES		
	1. *Boundaries*	Encapsulated or well-circumscribed	Poorly-circumscribed and irregular
	2. *Surrounding tissue*	Often compressed	Usually invaded
	3. *Size*	Usually small	Often larger
	4. *Secondary changes*	Occur less often	Occur more often
II.	MICROSCOPIC FEATURES		
	1. *Pattern*	Usually resembles the tissue of origin closely	Often poor resemblance to tissue of origin
	2. *Basal polarity*	Retained	Often lost
	3. *Pleomorphism*	Usually not present	Often present
	4. *Nucleo-cytoplasmic ratio*	Normal	Increased
	5. *Anisonucleosis*	Absent	Generally present
	6. *Hyperchromatism*	Absent	Often present
	7. *Mitoses*	May be present but are always typical mitoses	Mitotic figures increased and are generally atypical and abnormal
	8. *Tumour giant cells*	May be present but without nuclear atypia	Present with nuclear atypia
	9. *Chromosomal abnormalities*	Infrequent	Invariably present
	10. *Function*	Usually well maintained	May be retained, lost or become abnormal
III.	GROWTH RATE	Usually slow	Usually rapid
IV.	LOCAL INVASION	Often compresses the surrounding tissues without invading or infiltrating them	Usually infiltrates and invades the adjacent tissues
V.	METASTASIS	Absent	Frequently present
VI.	PROGNOSIS	Local complications	Death by local and metastatic complications

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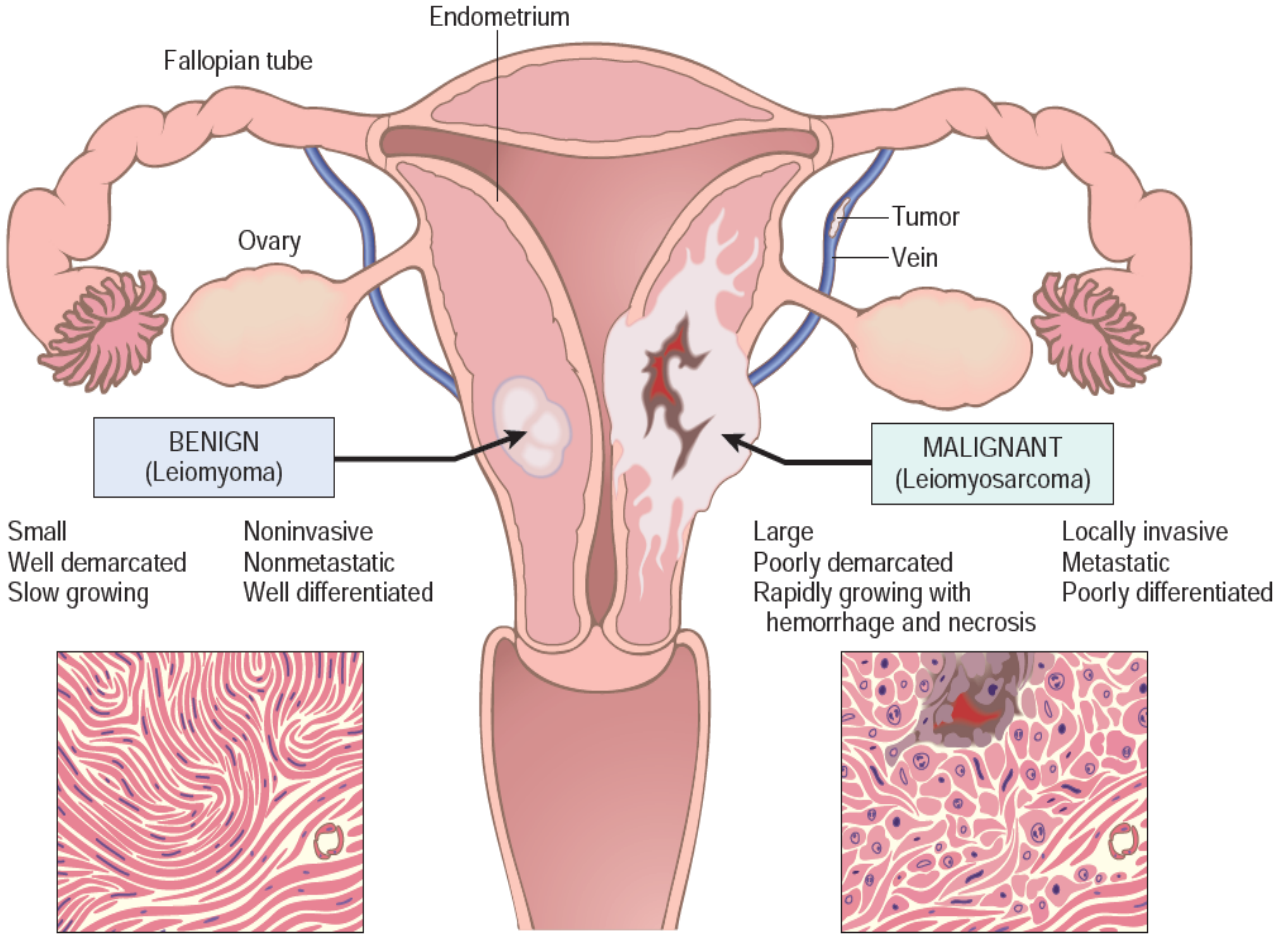

Figure 7-19 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of the same origin (leiomyosarcoma).

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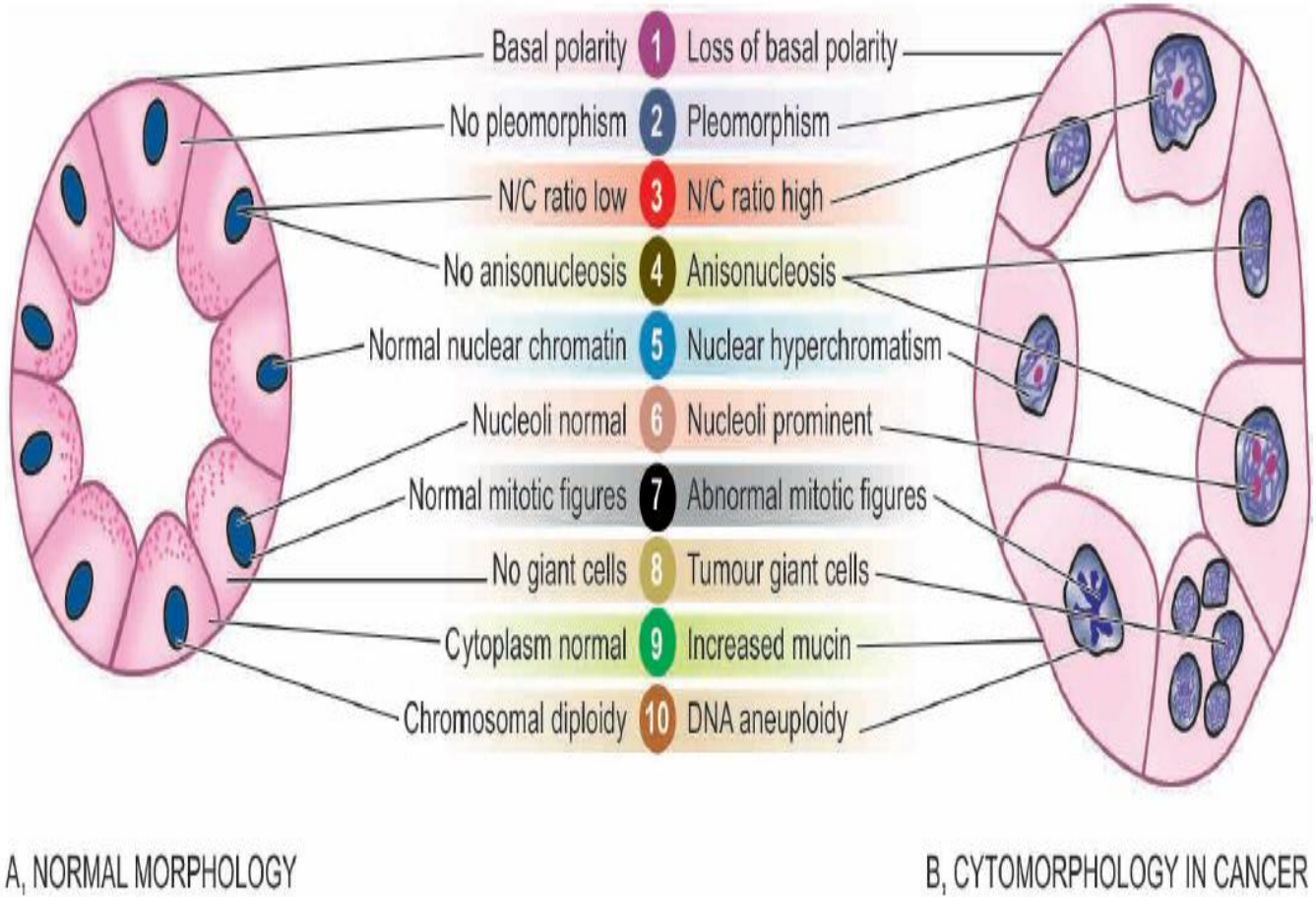
Basal polarity
1
Loss of basal polarity
No pleomorphism
2
Pleomorphism
N/C ratio low
3
N/C ratio high
No anisonucleosis
4
Anisonucleosis
Normal nuclear chromatin
5
Nuclear hyperchromatism
Nucleoli normal
6
Nucleoli prominent
Normal mitotic figures
7
Abnormal mitotic figures
No giant cells
8
Tumour giant cells
Cytoplasm normal
9
Increased mucin
Chromosomal diploidy
10
DNA aneuploidy
A, NORMAL MORPHOLOGY
B, CYTOMORPHOLOGY IN CANCER

III.	GROWTH RATE	Usually slow	Usually rapid
IV.	LOCAL INVASION	Often compresses the surrounding tissues without invading or infiltrating them	Usually infiltrates and invades the adjacent tissues
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	FEATURE	BENIGN	MALIGNANT
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Criteria	Benign	Malignant (cancer)
Differentiation	Well differentiated	Well differentiated to undifferentiated (anaplastic)
Growth limits	Limited, encapsulated	Unrestricted, no surrounding capsule
Growth rate	Usually slow	Often rapid, but can be slow
Invasivness	Non-invasive	Invasive
Metastasis	Non-metastatic	Metastatic
Mitotic figures	Rare	**Atypical, with increased number** *(PG/ 98)*
Cell size & shape	Uniform	Pleomorphism
Nuclear to cytoplasmic ratio	Normal (1:4 to 1:6)	Increased (1:1)
Stroma	Abundant	Often scanty
Cell orientation (Polarity)	Normal	Disorganized (loss of polarity)
Nuclear chromatin	Normal	Hyperchromatasia
Blood supply	Adequate	Often inadequate thus areas of necrosis

POLLS 3

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Scan or Click to watch
Neoplasia E01

Scan or Click to watch
Renal Pathology E02

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The most reliable feature of malignant tumor-

a) Local invasion
b) Metastasis
c) Rapid growth
d) Poor differentiation

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B

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Squamous cell carcinoma spreads commonly via -

a) Implantation
b) Hematogenous spread
c) Lymphatic spread
d) Trancoelomic spread

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c

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- Spread of carcinoma → Commonly by lymphatics
- Spread of sarcoma → Commonly hematogenous

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All of the following is involved in tumor metastasis cascade except -

a) Fibronectin
b) E-cadherin
c) Type IV collegenase
d) Tyrosine kinase

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D

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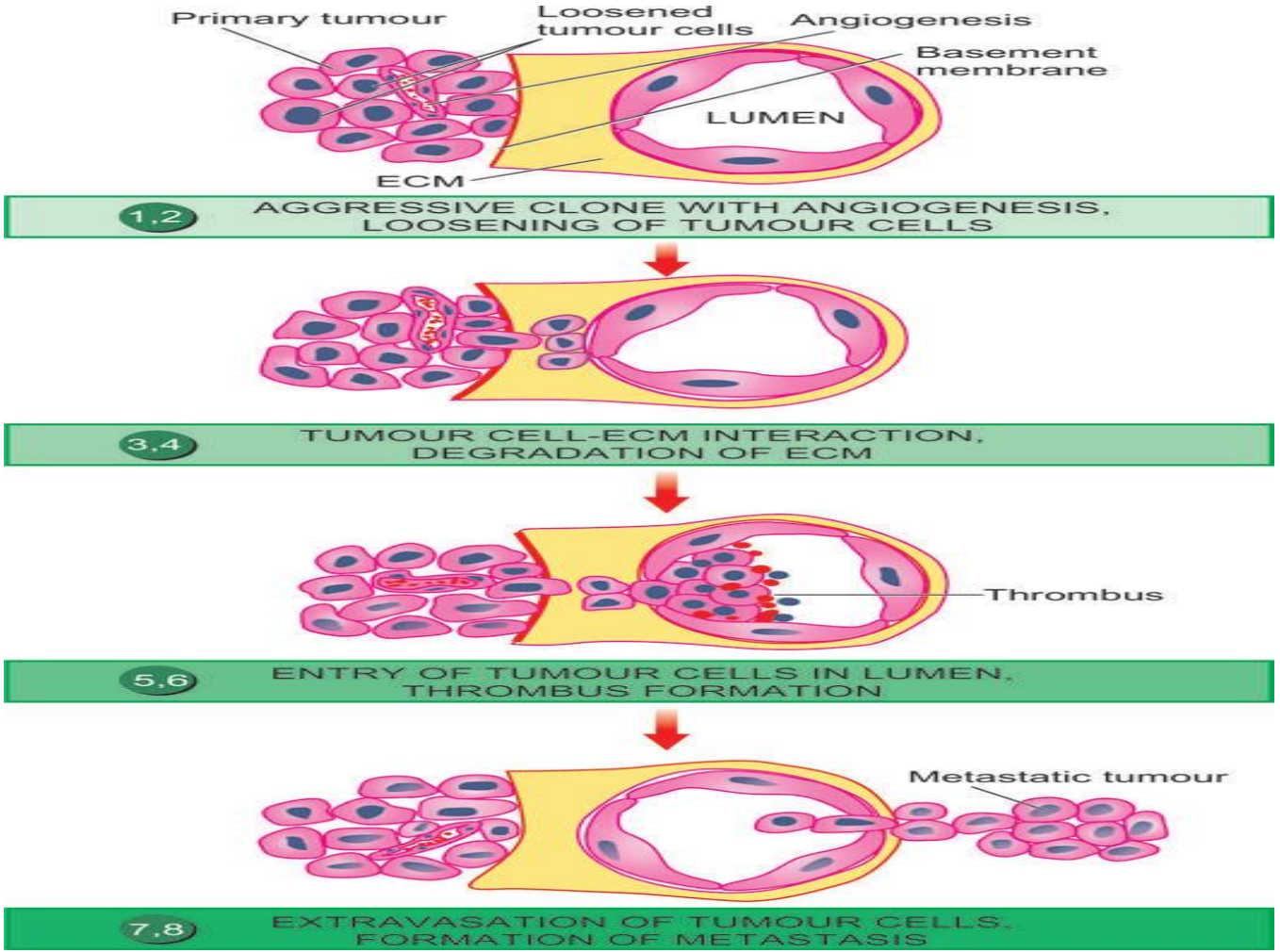
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5,6
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Metastatic tumour
7,8
EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

Which is the most common site of metastasis -

a) Lung
b) Bone
c) Liver
d) Brain

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c

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Carcinoma with no or minimal metastasis?

a) Squamous cell carcinoma
b) Basal cell carcinoma
c) Melanoma
d) Leydig's cell carcinoma

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Which of the following helps in differentiation of follicular carcinoma from follicular adenoma of thyroid gland?

(a) Hurthle cell change
(b) Lining of tall columnar and cuboidal cells
(c) Vascular invasion
(d) Increased mitoses

c

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Squamous cell carcinoma spreads by:

(a) Hematogenous route
(b) Lymphatic route
(c) Direct invasion
(d) All

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Sure sign of malignancy is:

(a) Mitoses
(b) Polychromasia
(c) Nuclear pleomorphism
(d) Metastasis

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D

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All the following malignant tumours metastasise except:

A. Synovial sarcoma
B. Malignant mesothelioma
C. Glioma
D. Neuroblastoma

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c

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Genetic regulators (genes)

Normal cell growth, 4 regulatory genes:

i) **Proto-oncogenes** are growth-promoting genes

ii) Anti-oncogenes or tumour suppressor genes are growth-inhibiting or growth suppressor genes.

iii) Apoptosis regulatory genes control the programmed cell death.

iv) DNA repair genes regulate repair of DNA damage that has occurred during mitosis and also control the damage to proto-oncogenes and antioncogenes.

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Genetic regulators (genes)

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ii) **Anti-oncogenes or tumour suppressor genes** are growth-inhibiting or growth suppressor genes.

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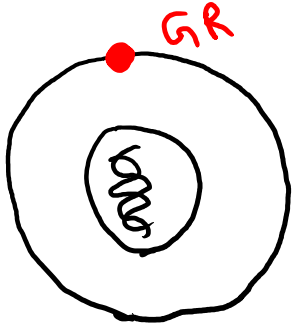
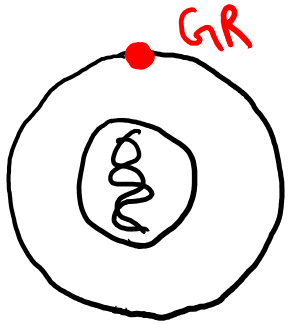
NORMAL CELL





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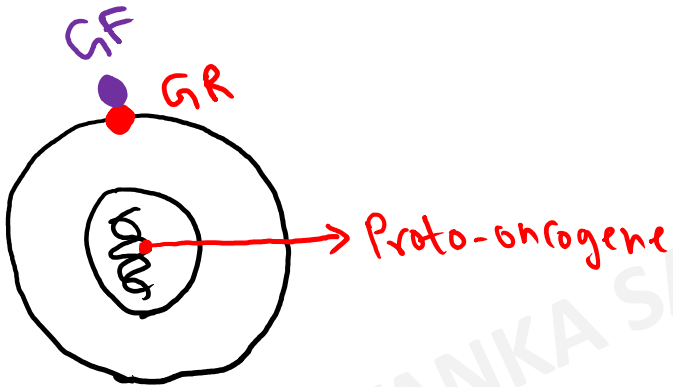
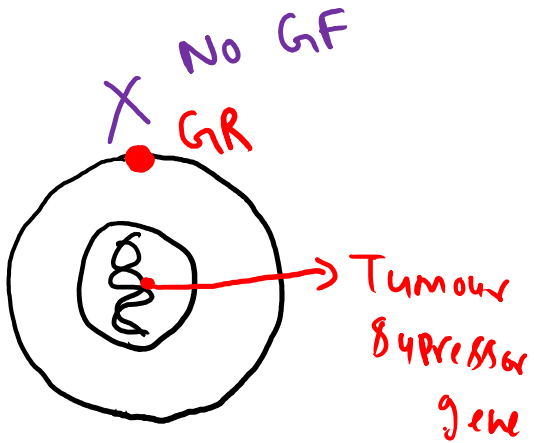
NORMAL CELL





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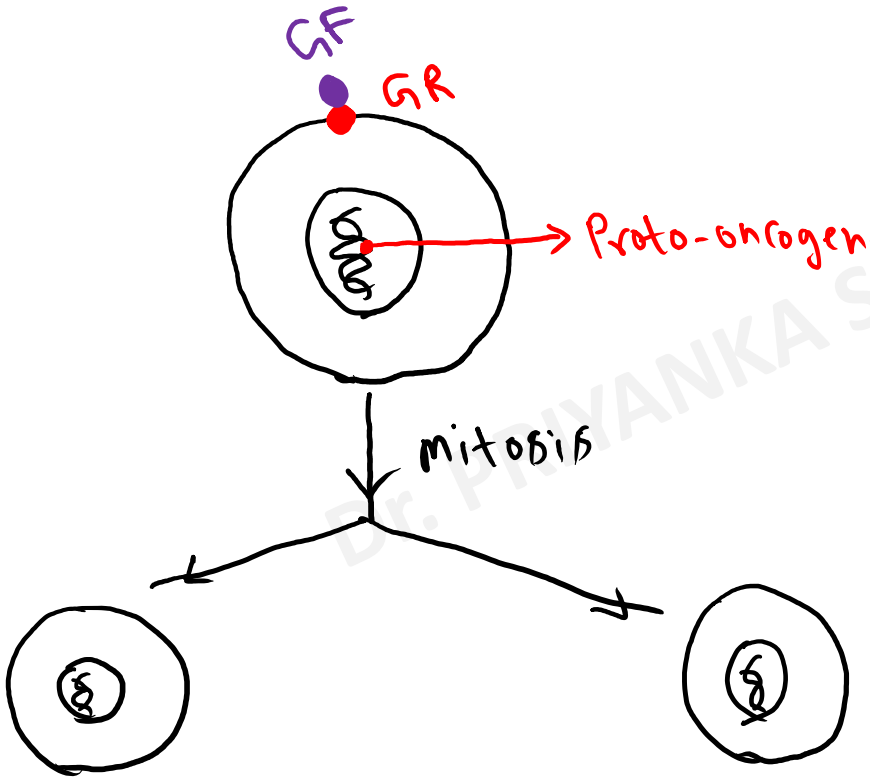
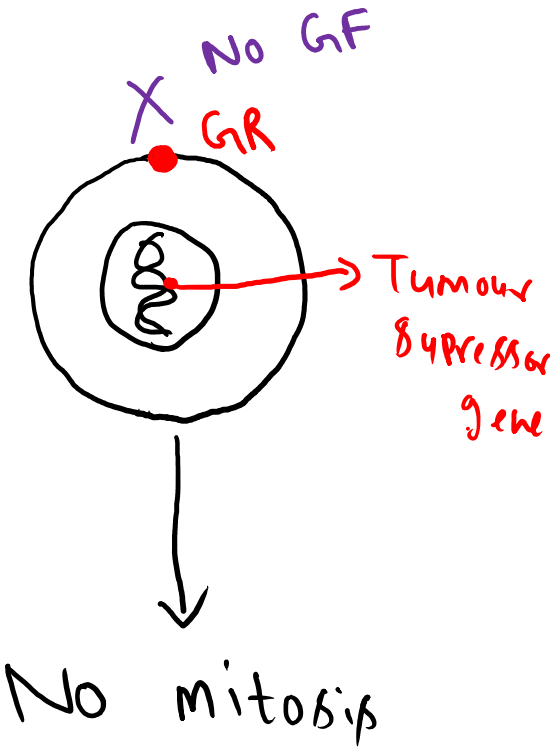
NORMAL CELL





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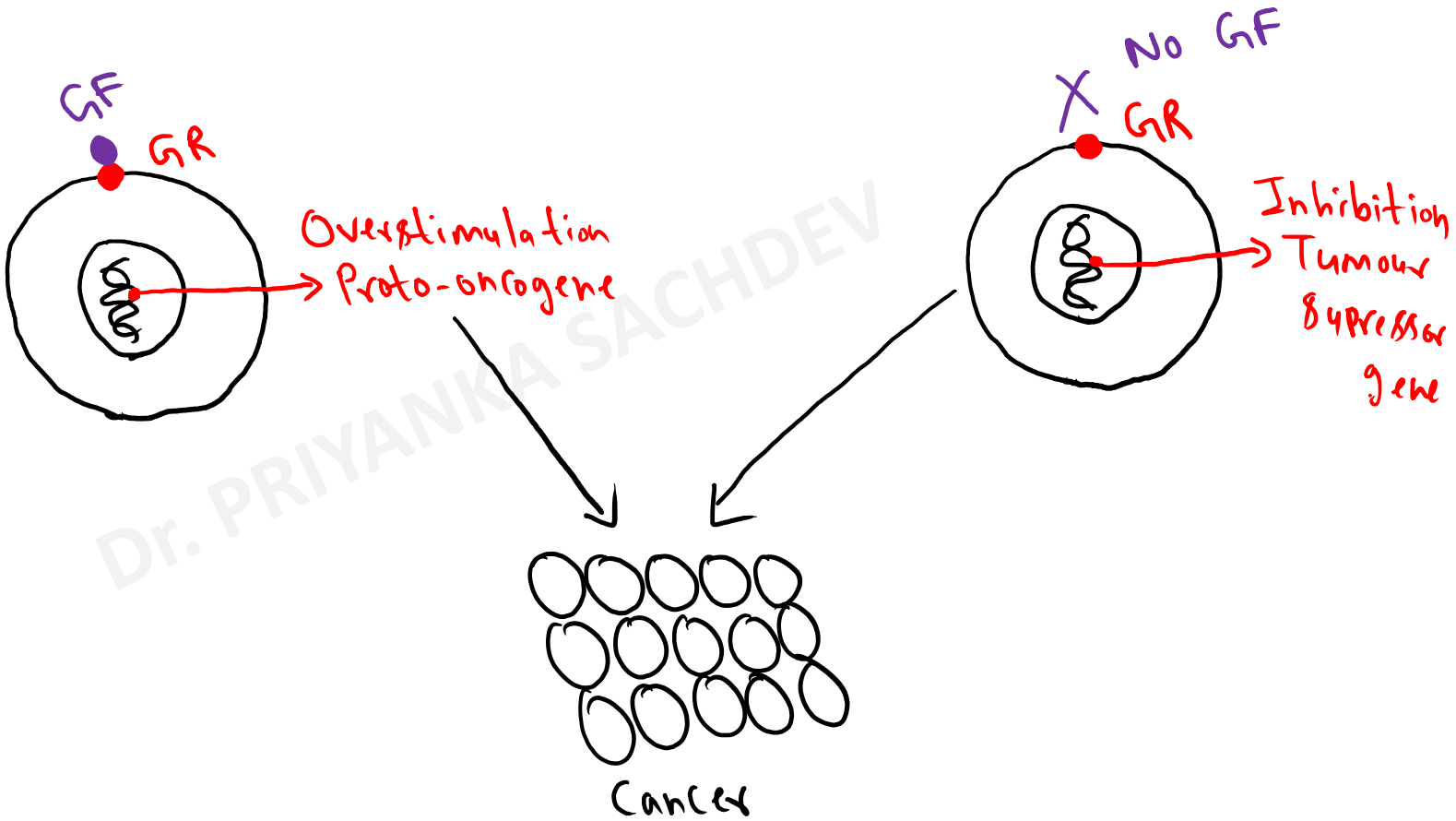
NORMAL CELL



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In cancer

i) Overstimulation of proto-oncogenes

ii) Inhibition of tumour-suppressor genes

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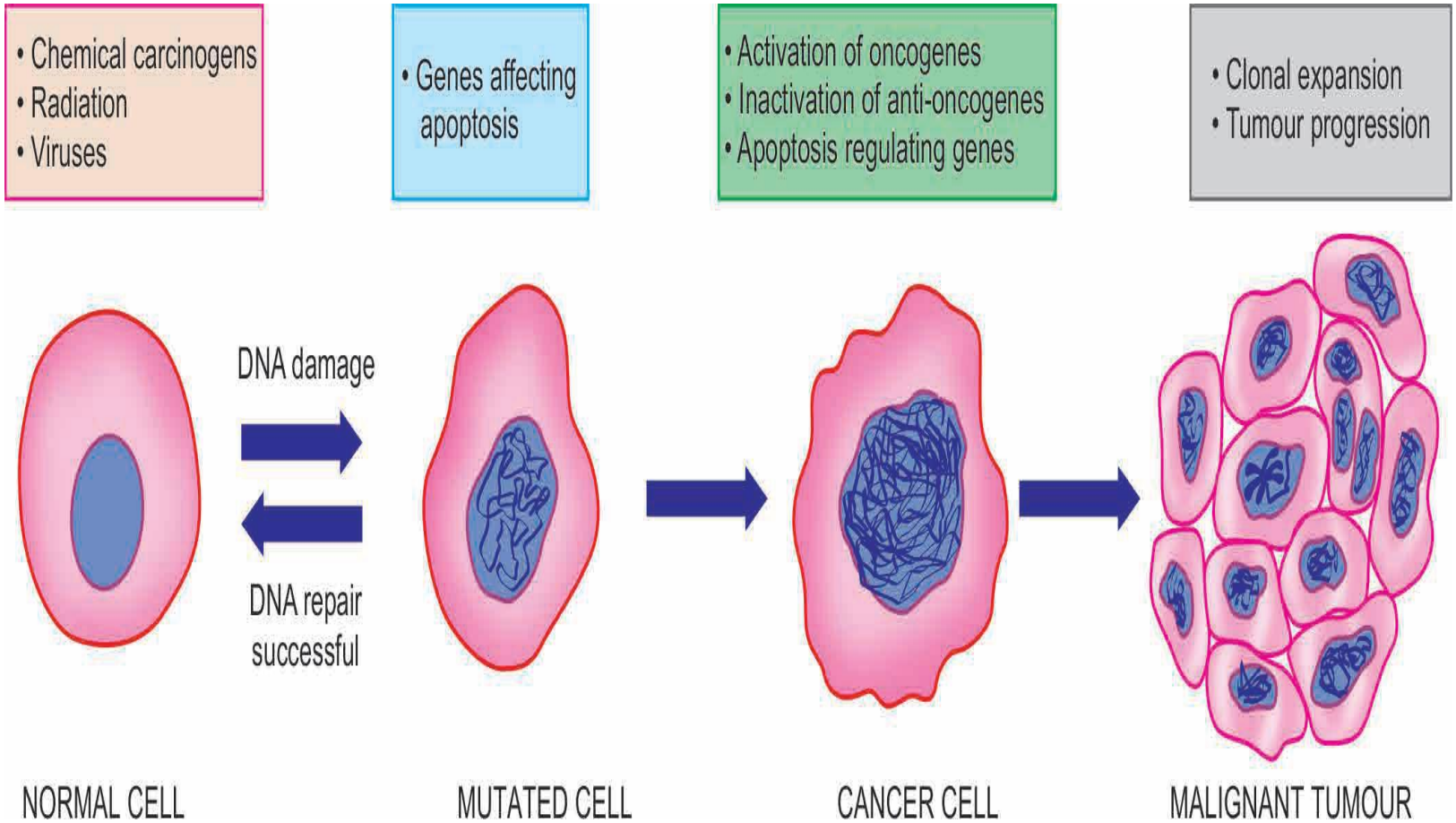
• Chemical carcinogens
• Radiation
• Viruses
• Genes affecting apoptosis
• Activation of oncogenes
• Inactivation of anti-oncogenes
• Apoptosis regulating genes
• Clonal expansion
• Tumour progression
DNA damage
DNA repair successful
NORMAL CELL
MUTATED CELL
CANCER CELL
MALIGNANT TUMOUR

In cancer

i) Overstimulation of proto-oncogenes

ii) Inhibition of tumour-suppressor genes

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Activation of Proto-Oncogenes

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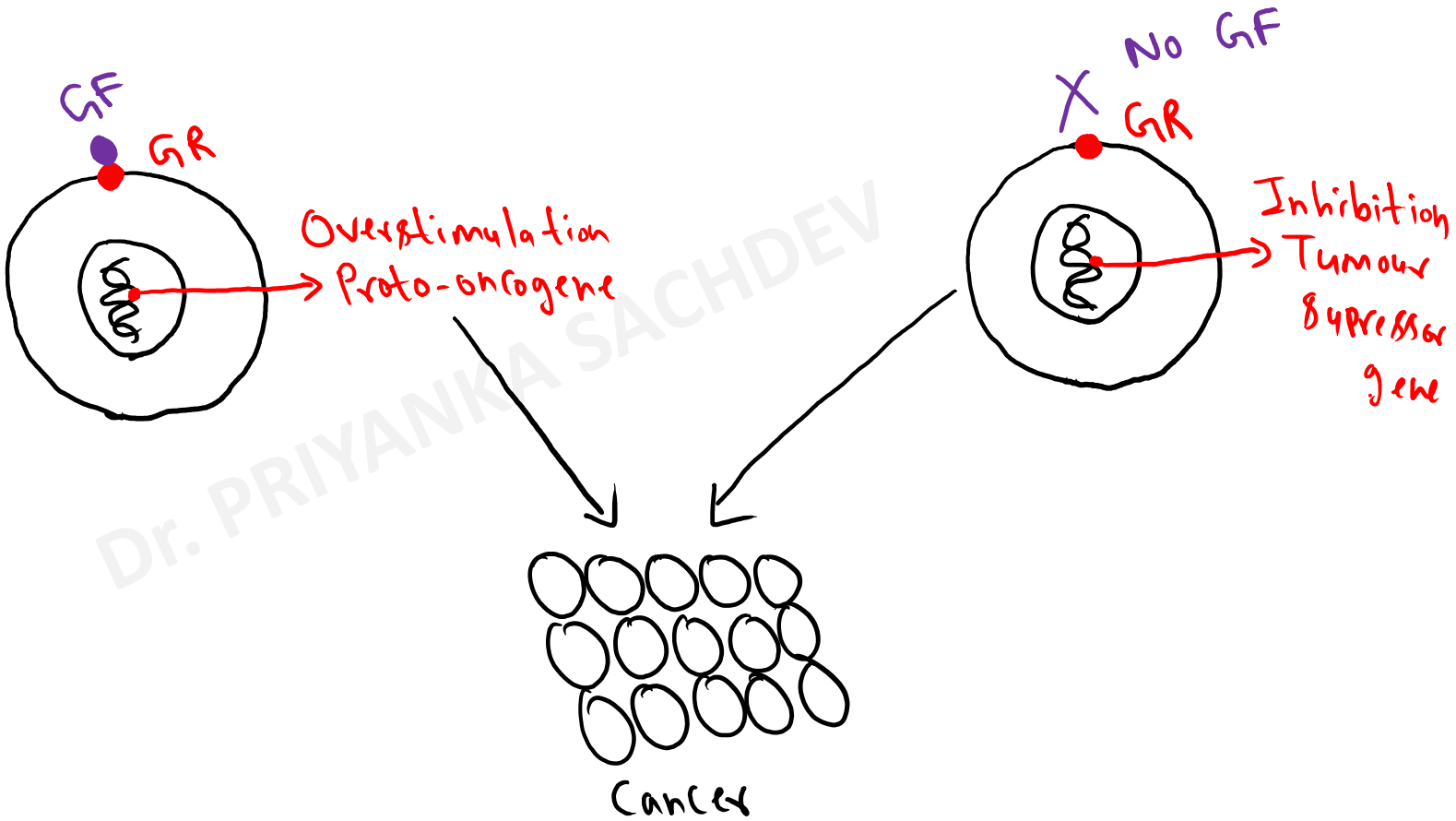
NORMAL CELL



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Proto-oncogenes

- Proto-oncogenes were discovered by **Harold Varmus and Michael Bishop.**

- **Normal genes** required for cell proliferation
- They act under proper **physiological stimuli**
- Without physiological stimuli they will be silent and there is no replication.

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Oncogenes

- **Derived from mutation of proto-oncogenes**
-
- When, due to mutation, proto- oncogenes become autonomous ie. promote cell growth **without any physiological stimulus,** it acts as oncogene.

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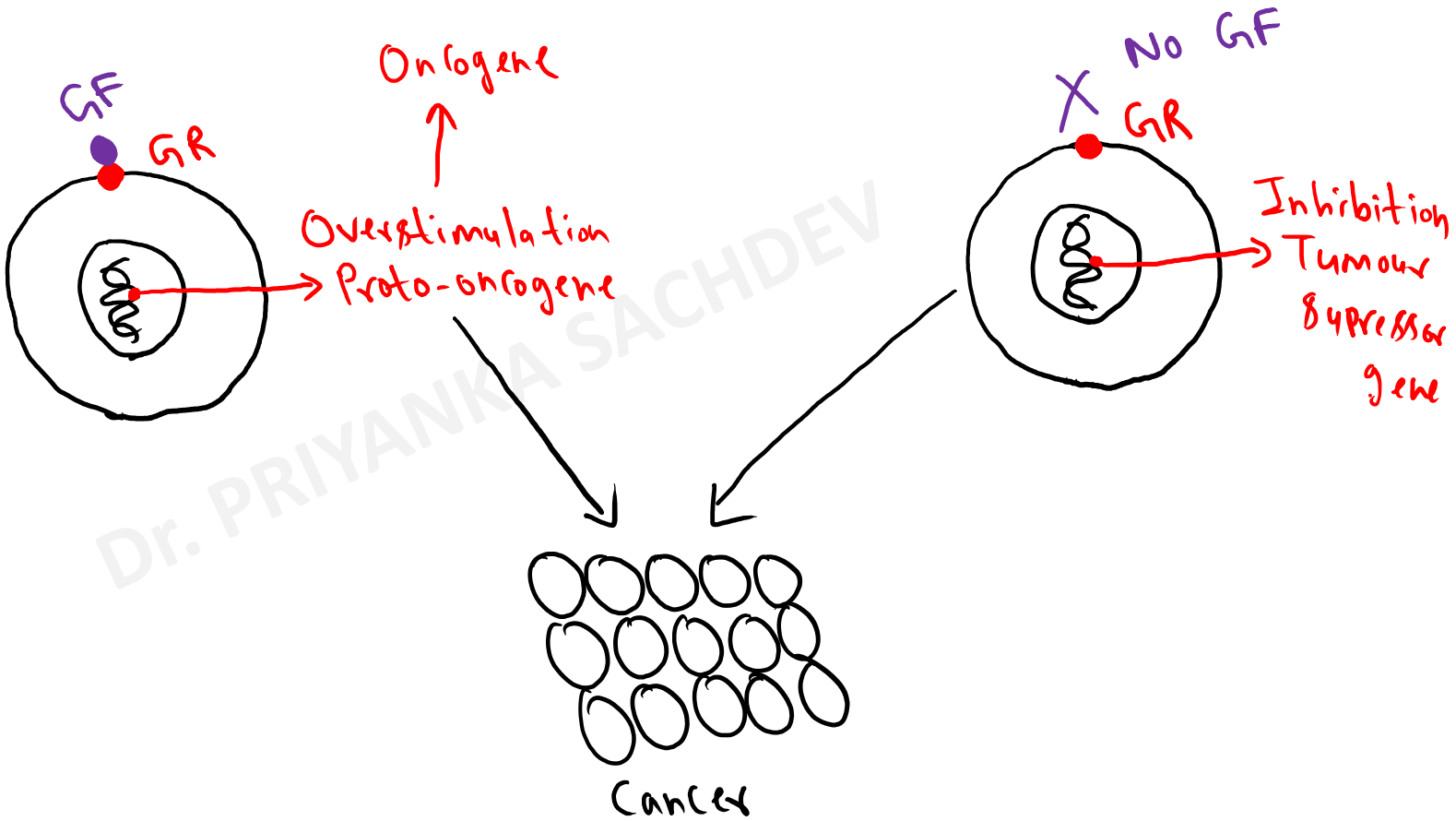
NORMAL CELL



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- Infact oncogene and protooncogene is the same,

- In normal cell it acts as protooncogen while in cancer cell it acts as oncogene

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Proto-oncogenes (Normal genes required for cell proliferation and differentiation)

↓ **Mutation**

Oncogenes (Genes promoting autonomous cell growth in cancer cells)

↓

Oncoproteins (Proteins lacking regulatory control and responsible for promoting cell growth)

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Transformation of **proto-oncogene to oncogene** occur by 3 mechanisms:

- **Point mutations**
- **Chromosomal translocations**
- **Gene amplification**

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CLASSIFICATION

5 classes→

- i) Growth factors
- ii) Receptors of growth factors
- iii) Cytoplasmic signal transduction proteins
- iv) Nuclear transduction factors
- v) Cell regulatory proteins

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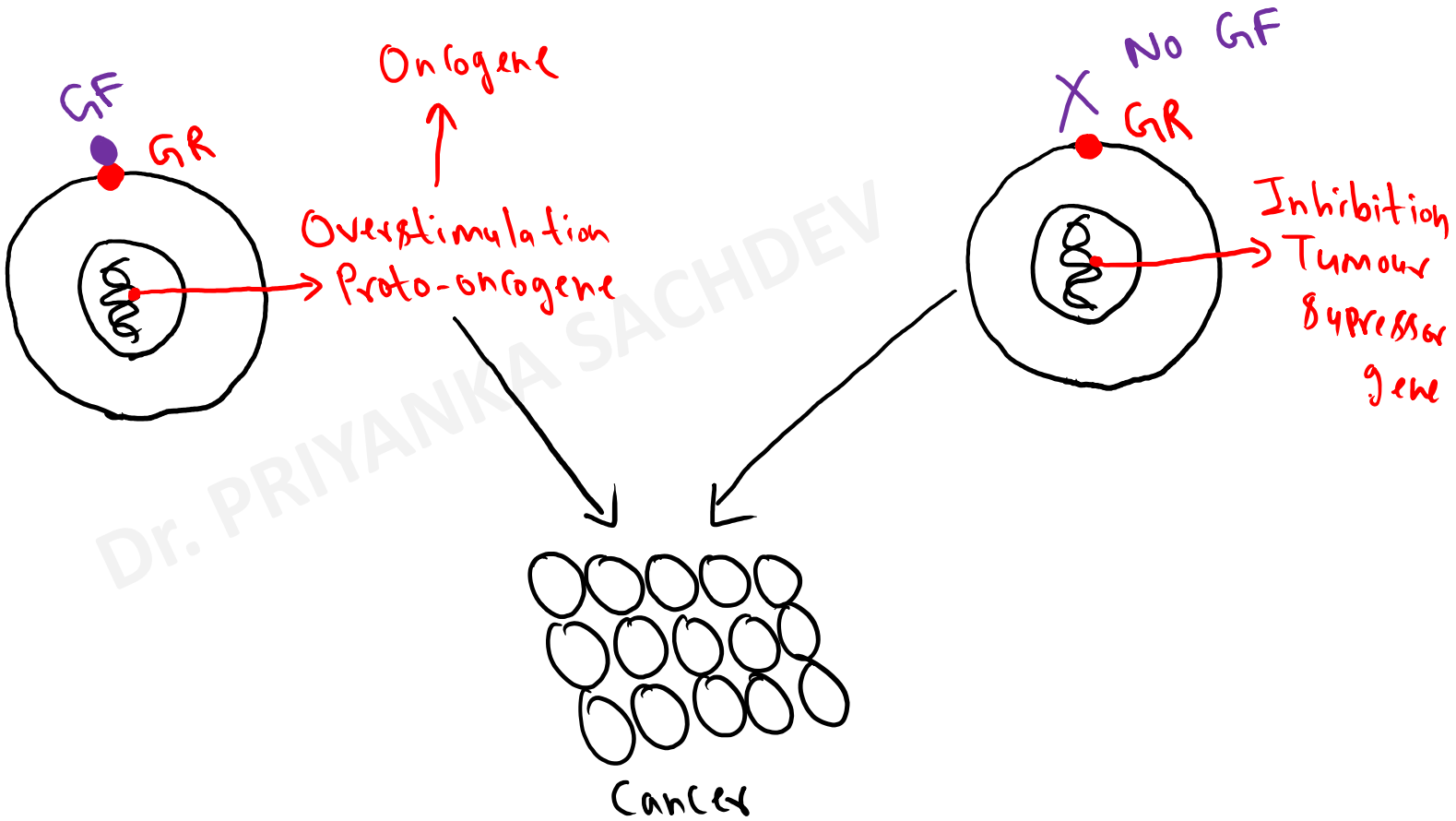
NORMAL CELL



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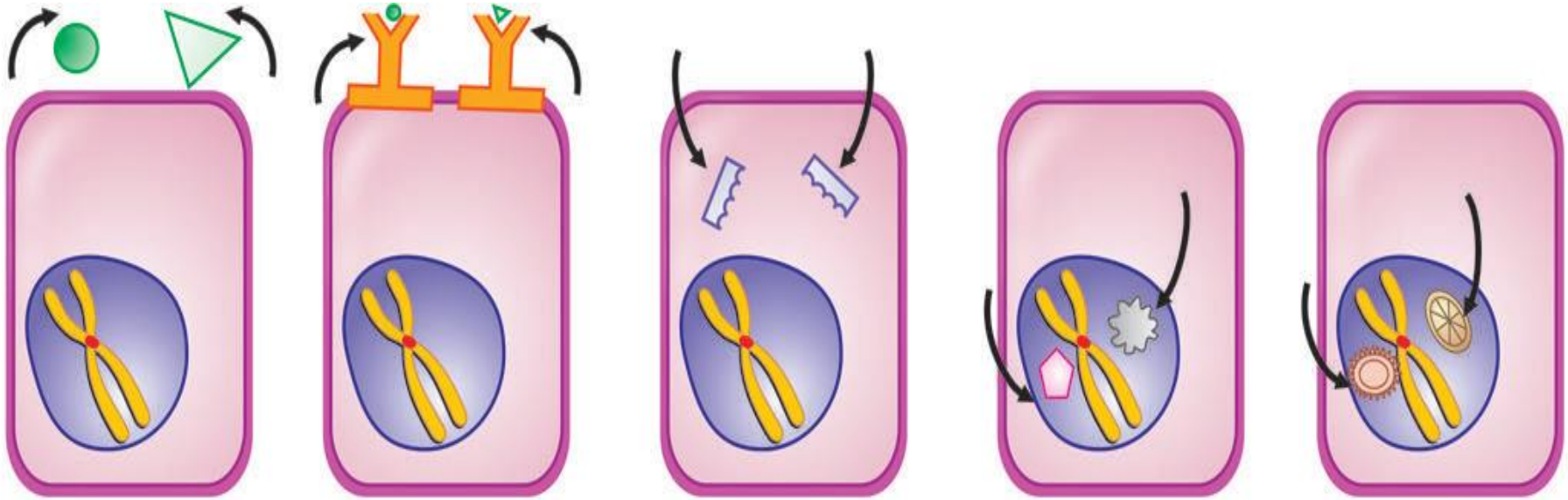

GROWTH FACTORS	RECEPTORS FOR GFs	CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS	NUCLEAR TRANSCRIPTION FACTORS	CELL CYCLE REGULATORY PROTEINS
i) PDGF-β ii) TGF-α iii) FGF iv) c-MET	i) EGF-R ii) c-KIT -R iii) RET-R iv) FMS-like	I) Mutated RAS ii) ABL-BCR	i) C-MYC ii) N-MYC iii) L-MYC	i) Cyclin D ii) Cyclin E iii) CDK4

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	TYPE	PROTO-ONCOGENE	MECHANISM	ASSOCIATED HUMAN TUMOURS
1.	GROWTH FACTORS			
	i) *PDGF-β*	*SIS*	Overexpression	Gliomas, sarcoma
	ii) *TGF-α*	*RAS*	Overexpression	Carcinomas, astrocytoma
	iii) *FGF*	*HST-1* INT-2	Overexpression Amplification	Bowel cancers Breast cancer
	iv) *c-MET*	HGF	Overexpression	Follicular carcinoma thyroid
2.	RECEPTORS FOR GROWTH FACTORS			
	i) *EGF* receptors	*ERB B1 (HER 1)* ERB B2 (*HER 2/neu)*	Overexpression Amplification	Squamous cell carcinoma lung, glioblastoma Ca breast, ovary, stomach, lungs
	ii) *c-KIT* receptor (Steel factor)	c-KIT	Point mutation	GIST
	iii) RET receptor	RET	Point mutation	MEN type 2A and type 2B, medullary ca thyroid
	iv) FMS-like tyrosine kinase receptor	FLT-3 gene	Point mutation	Acute myeloid leukaemia
3.	CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS			
	GTP-bound	*RAS*	Point mutation	Common in 1/3rd human tumours, Ca lung, colon, pancreas
	Non-GF receptor tyrosine kinase	*ABL-BCR*	Translocation	CML, acute leukaemias
4.	NUCLEAR TRANSCRIPTION FACTORS			
	C-MYC	MYC	Translocation	Burkitt's lymphoma
	N-MYC	*MYC*	Amplification	Neuroblastoma, small cell Ca lung
	L-MYC	*MYC*	Amplification	Small cell Ca lung
5.	CELL CYCLE REGULATORY PROTEINS			
	Cyclins	*Cyclin D* *Cyclin E*	Translocation Overexpression	Ca breast, liver, mantle cell lymphoma Ca breast
	CDKs	*CDK4*	Amplification	Glioblastoma, melanoma, sarcomas

RAS gene

- RAS protein is **signal transducing protein**

- Point mutation of RAS family genes is the single **most common abnormality of Proto-oncogenes** in human tumor.

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2 scenarios

- Normally
- Mutation

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NORMALLY

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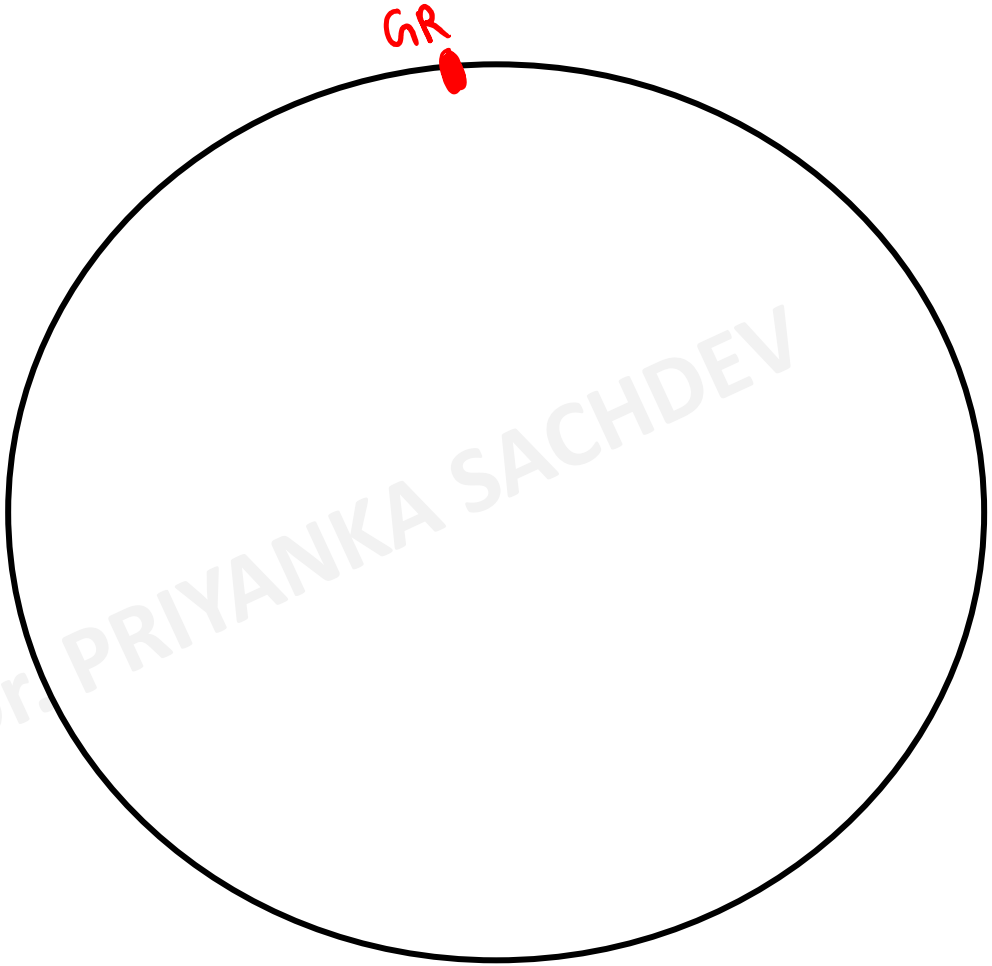

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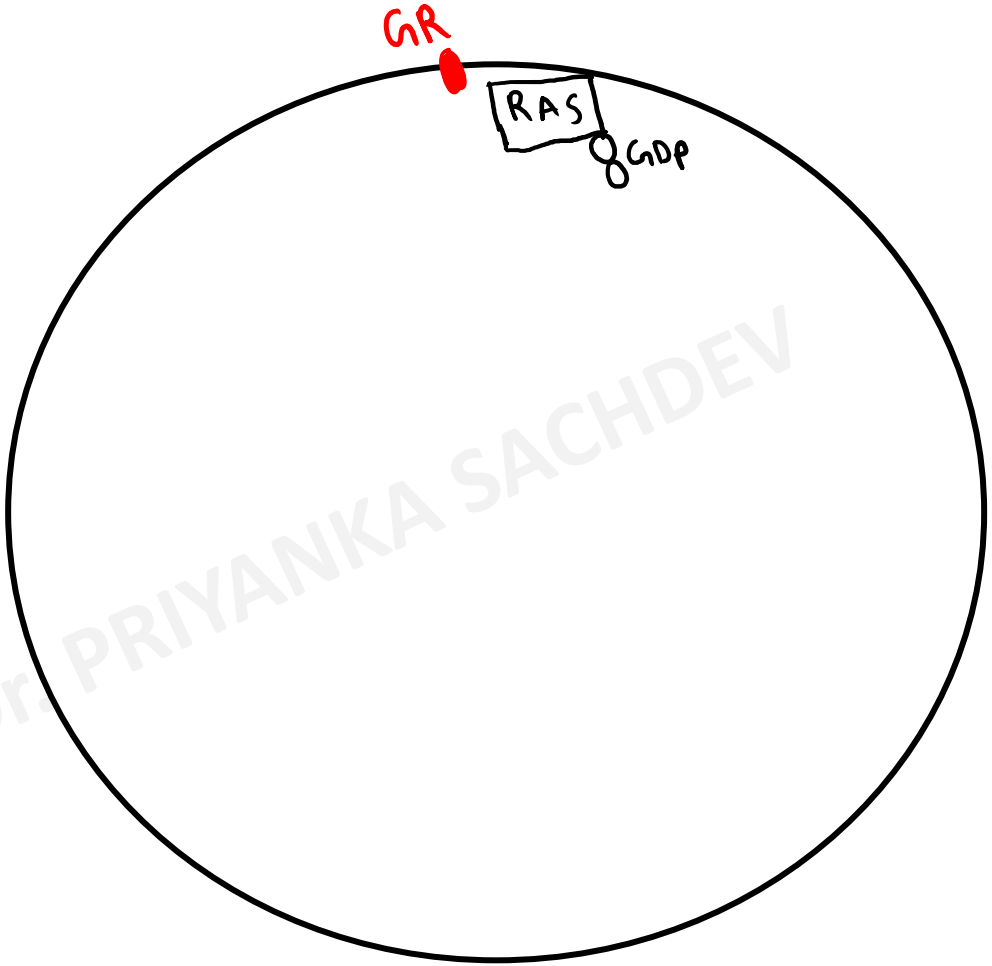

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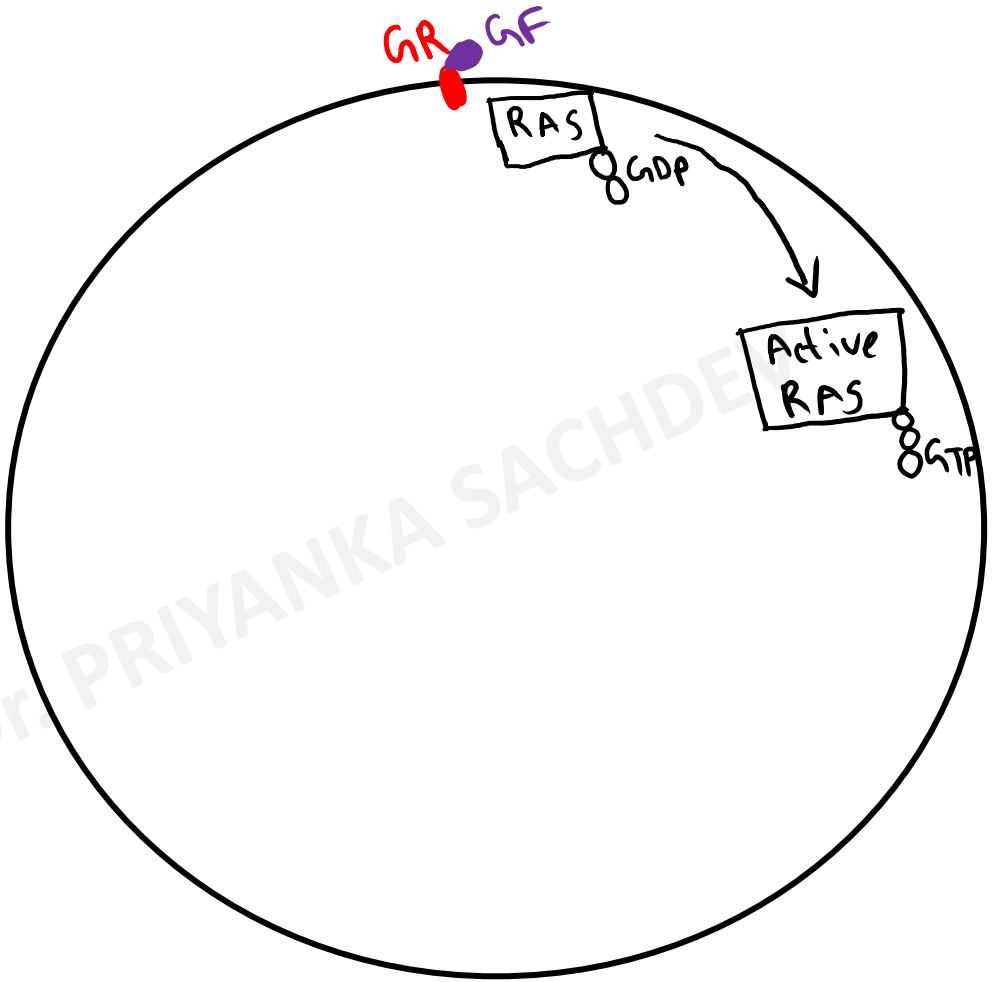

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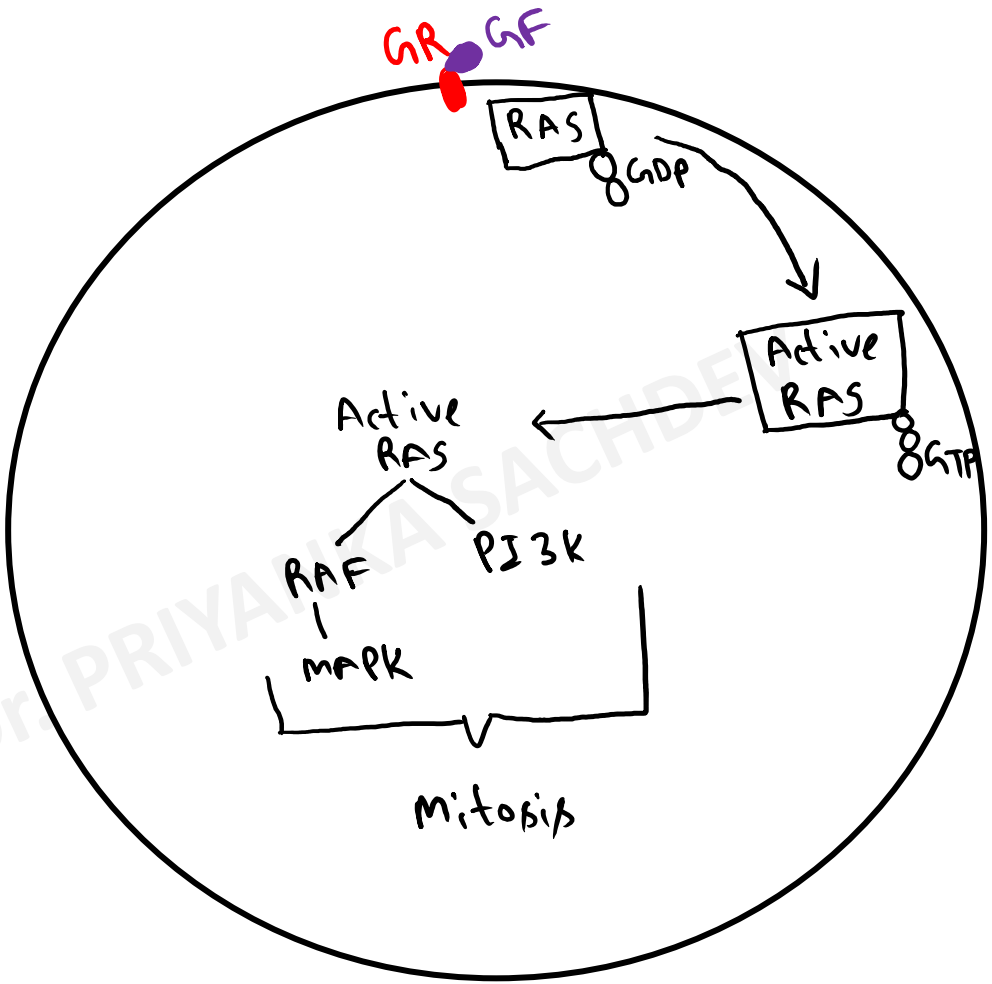

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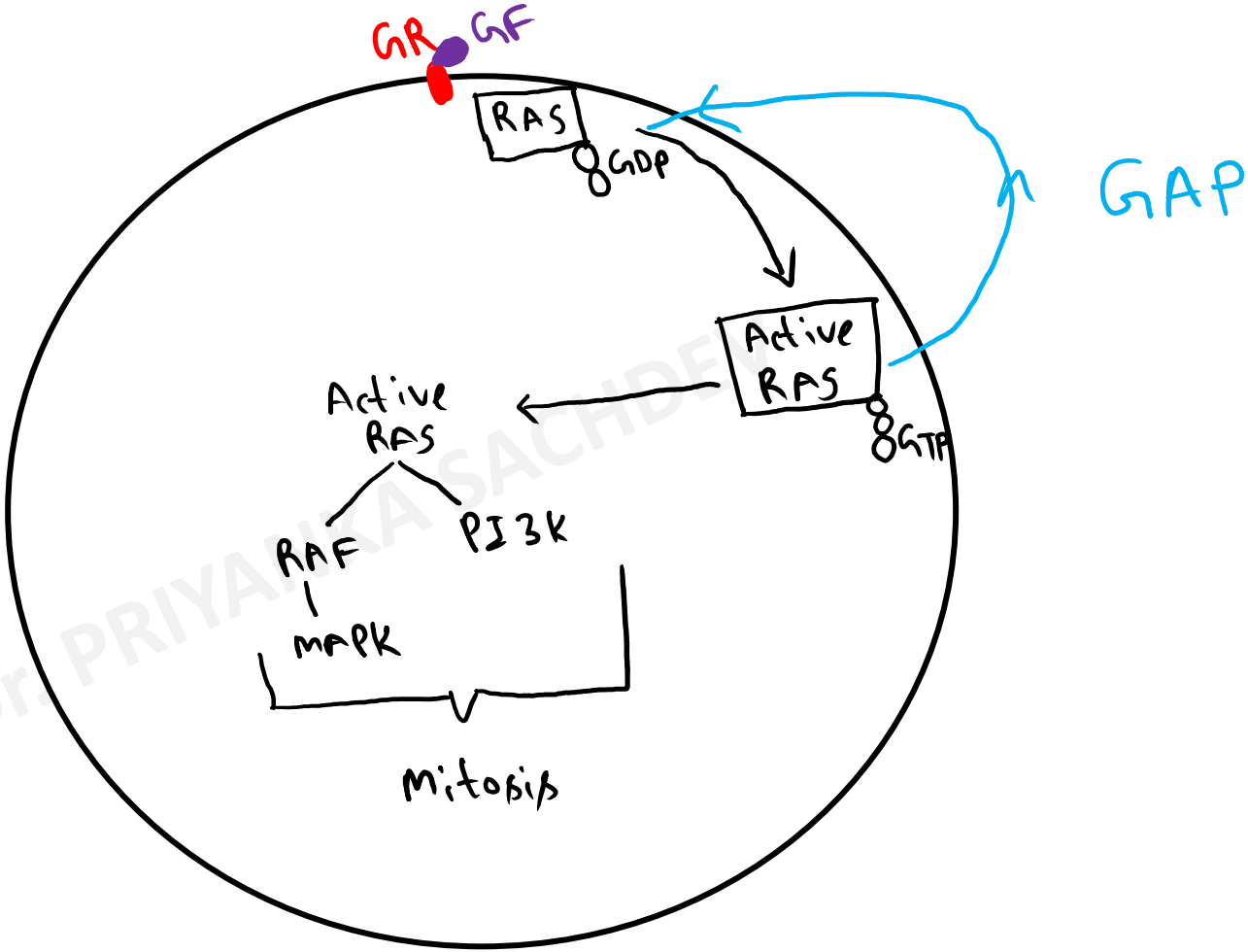

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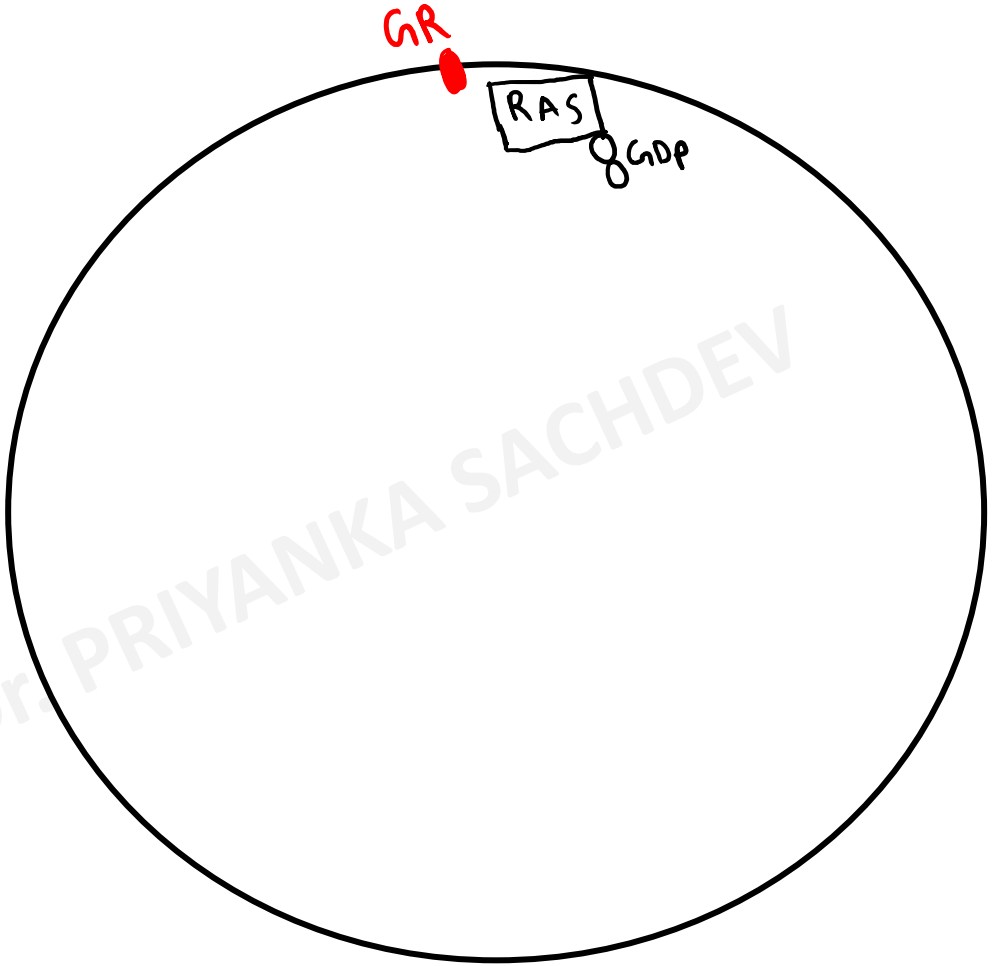

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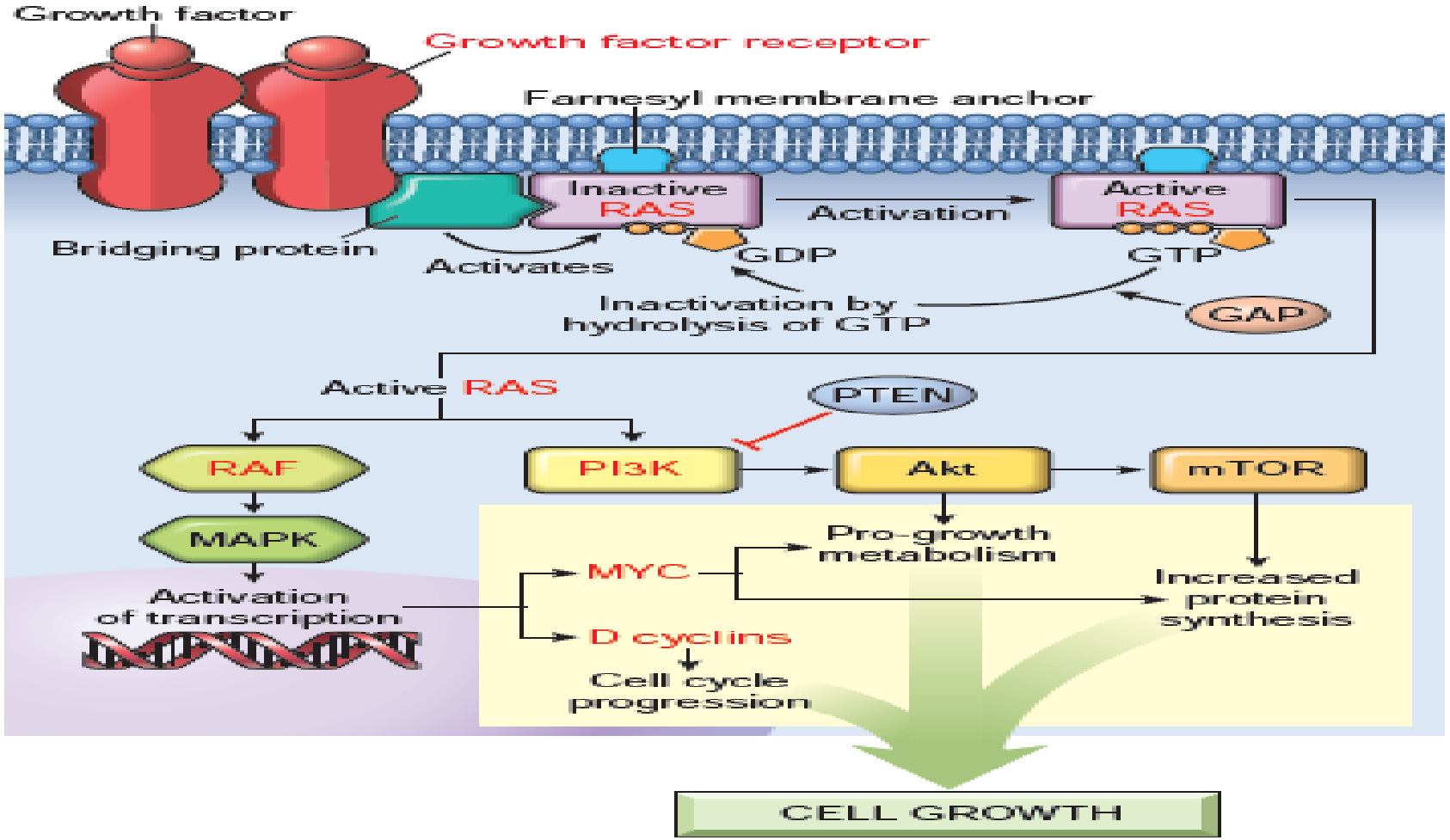
Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
Bridging protein
Activates
GDP
GTP
Inactivation by hydrolysis of GTP
GAP
Active RAS
PTEN
RAF
PI3K
Akt
mTOR
MAPK
Pro-growth metabolism
MYC
Increased protein synthesis
Activation of transcription
D cyclins
Cell cycle progression
CELL GROWTH

In Inactive state RAS proteins bind GDP

↓

Growth factors

↓

RAS proteins become activated by exchanging GDP for GTP

↓

Activated RAS recruits RAF-1 and also activates PI3K

↓

Mitosis

↓

GTPase Activating Proteins (GAP)

↓

GTP breaks into GDP

↓

RAS Back to inactive state (Activated state is transient)

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2 scenarios

- Normally
- Mutation

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MUTATION

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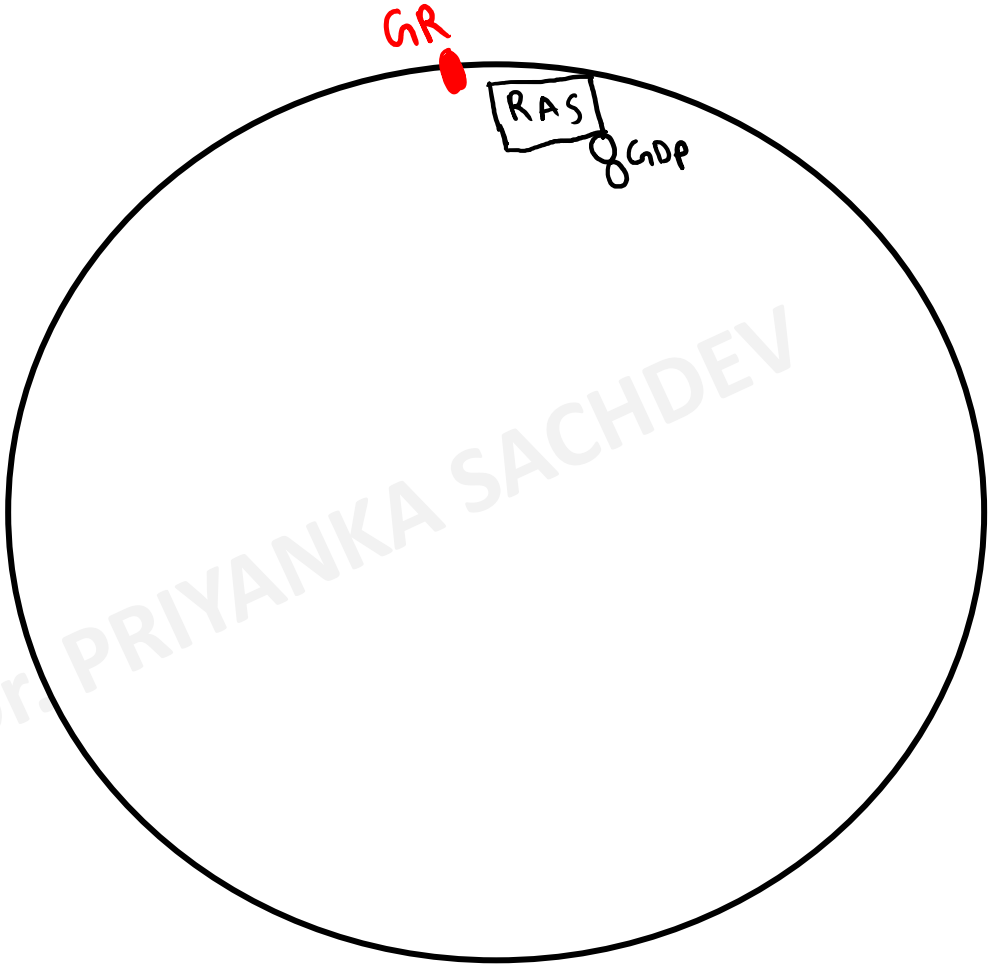

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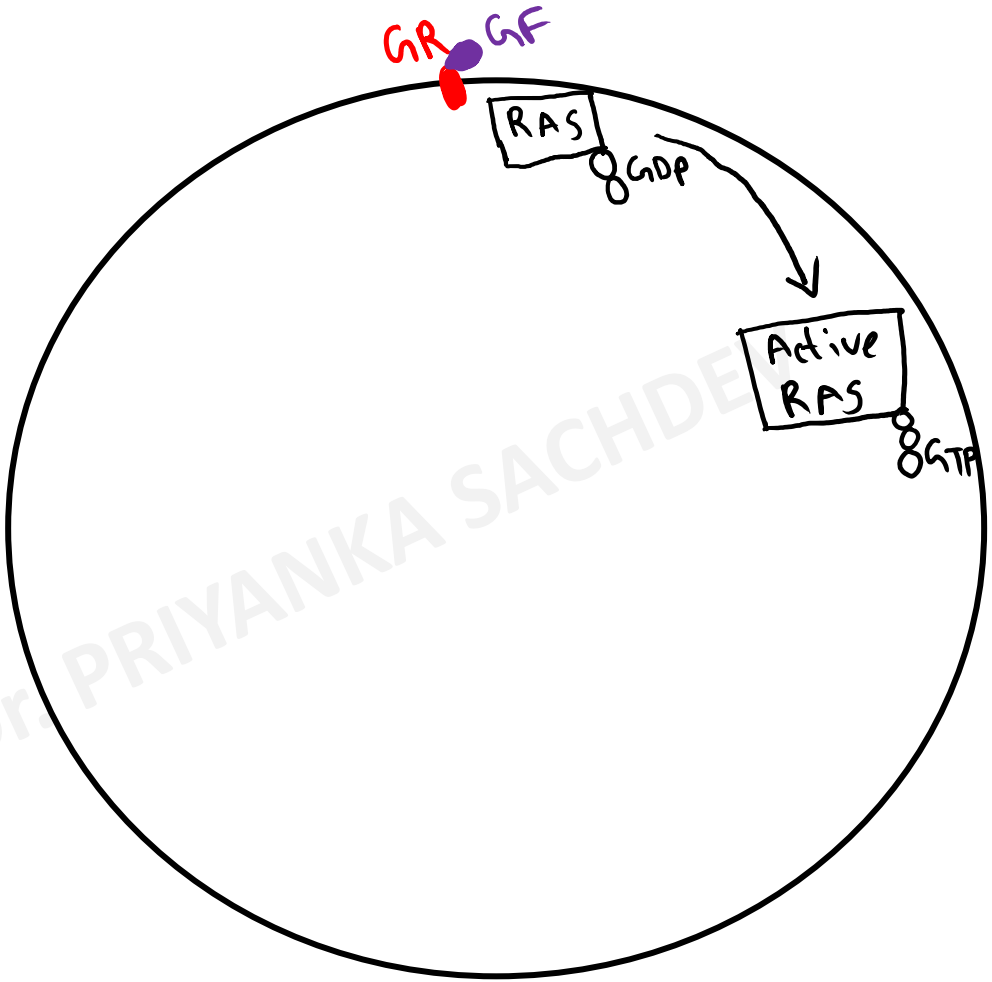

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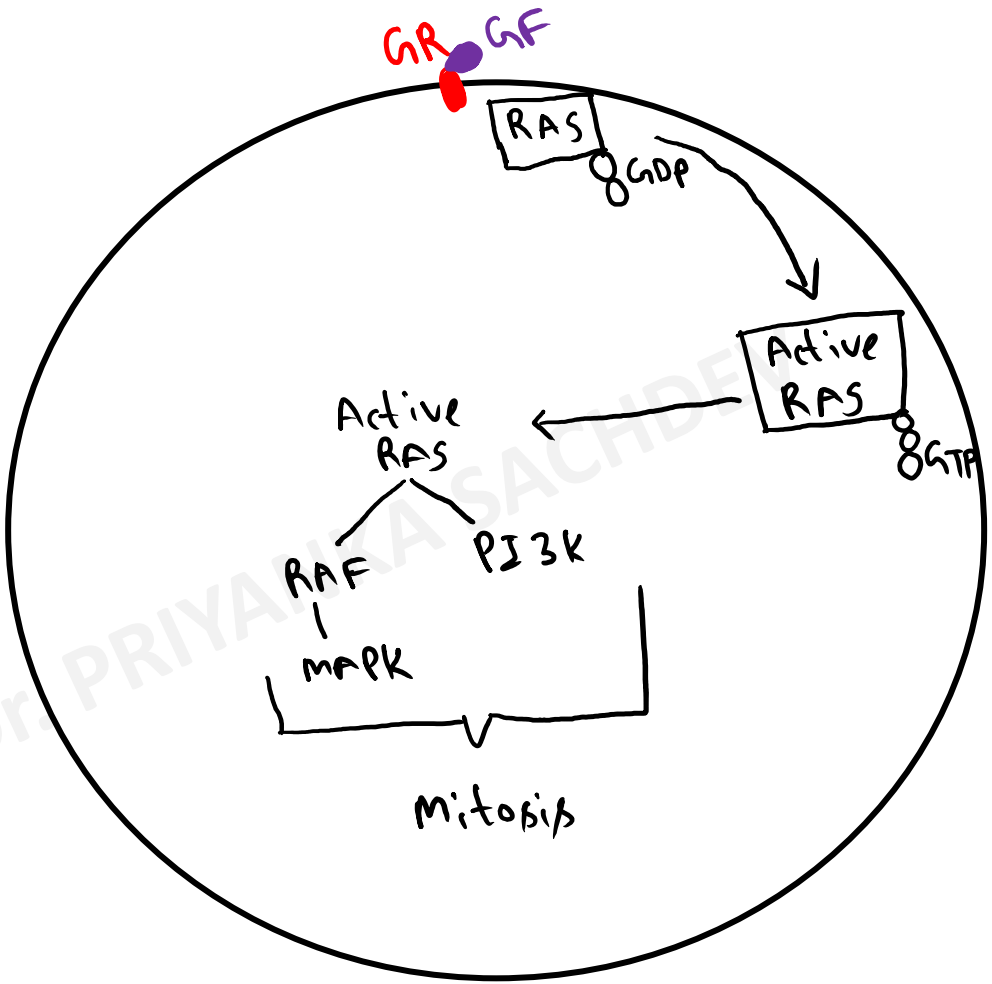

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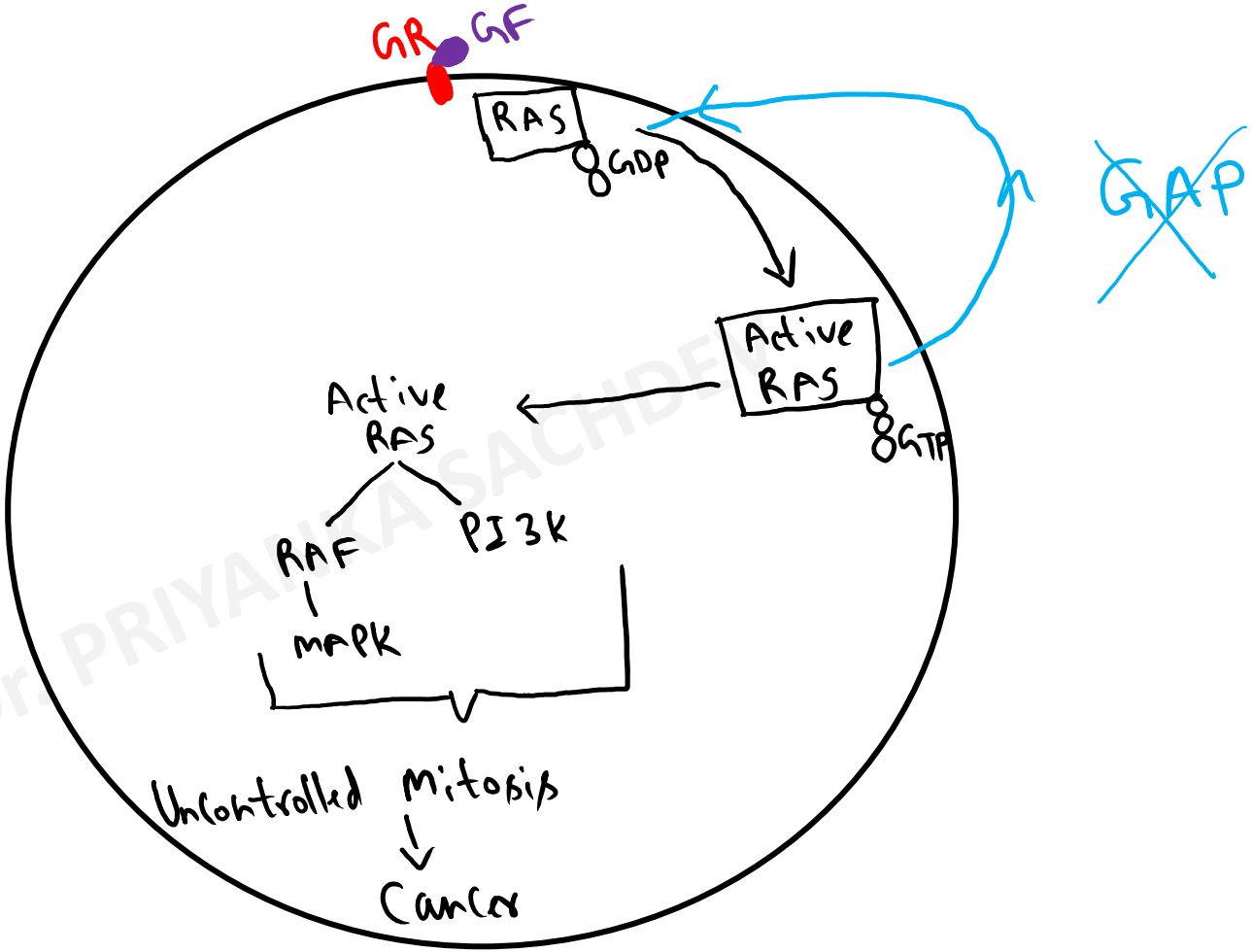

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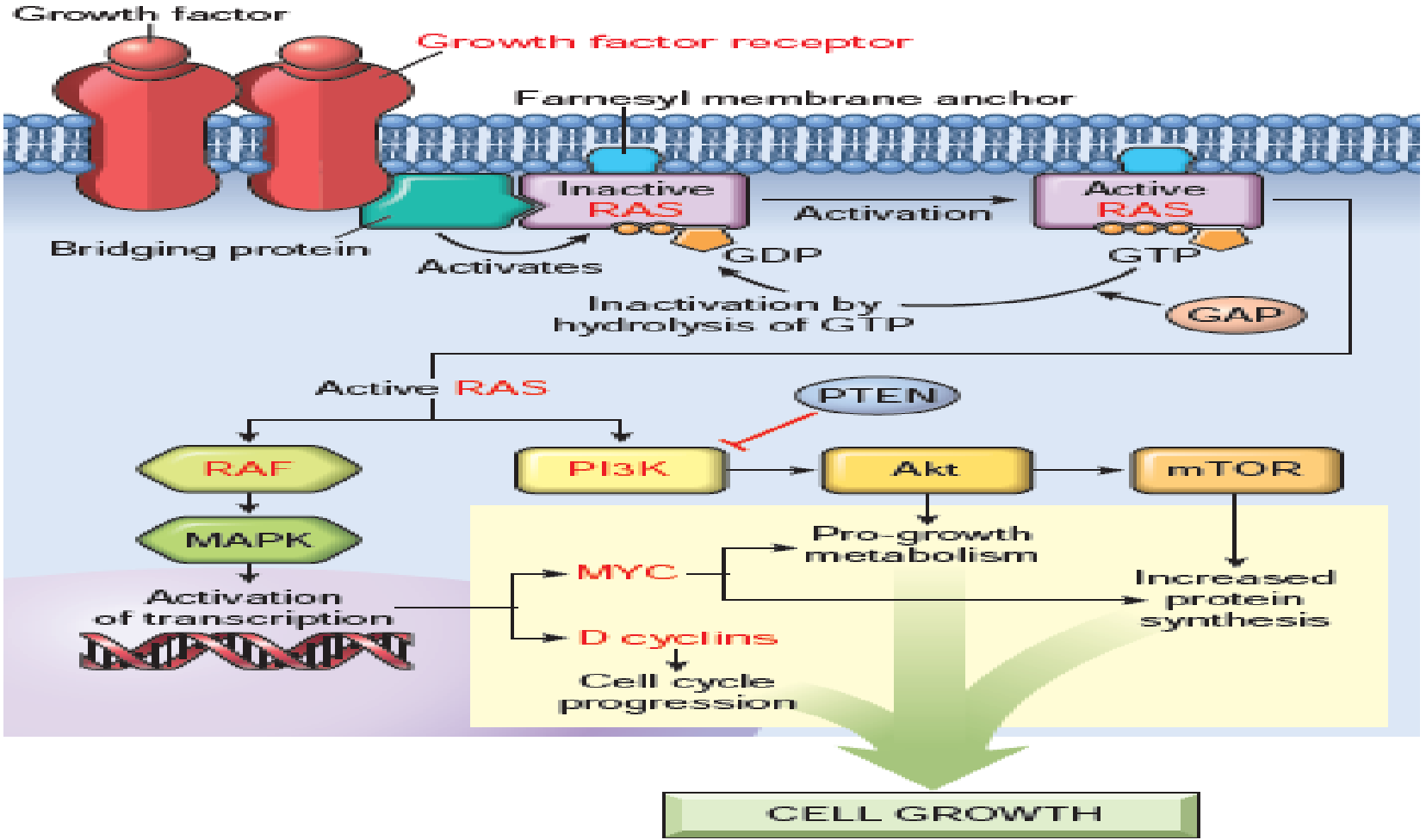
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PTEN
RAF
PI3K
Akt
mTOR
MAPK
Pro-growth metabolism
MYC
Increased protein synthesis
Activation of transcription
D cyclins
Cell cycle progression
CELL GROWTH

Mutation in the RAS gene

↓

GTPase Activating Proteins (GAP) not working

↓

GTPase acitivity cannot be increased

↓

No breakdown of GTP

↓

Permanent activation of RAS

↓

Uncontrolled mitosis

↓

Cancer

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EXAMPLES

K – RAS	Colon, lung and pancreatic tumors
N – RAS	Melanoma, blood tumors (AML)
H – RAS	Bladder and kidney tumors

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CLASSIFICATION

5 classes→

- i) Growth factors
- ii) Receptors of growth factors
- iii) Cytoplasmic signal transduction proteins
- iv) Nuclear transduction factors
- v) Cell regulatory proteins

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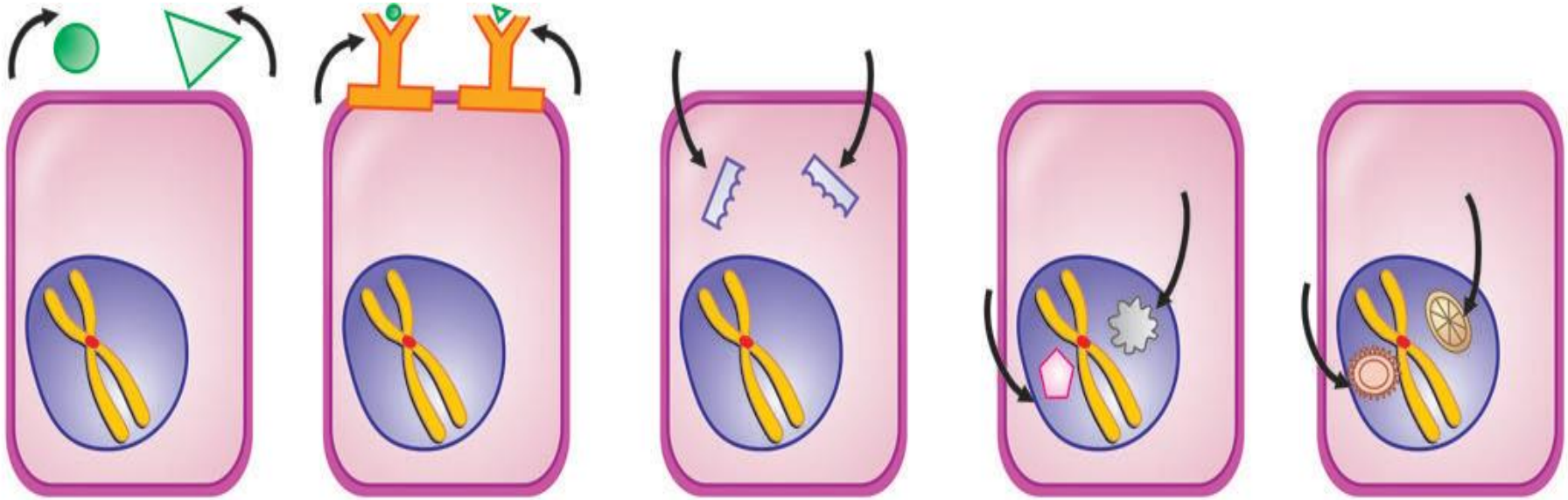

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ABL-BCR hybrid gene

- ABL gene is a protooncogene having tyrosine kinase activity.

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NORMALLY

- ABL gene → normal location on chromosome 9

- BCR gene→normal location on chromosome 22

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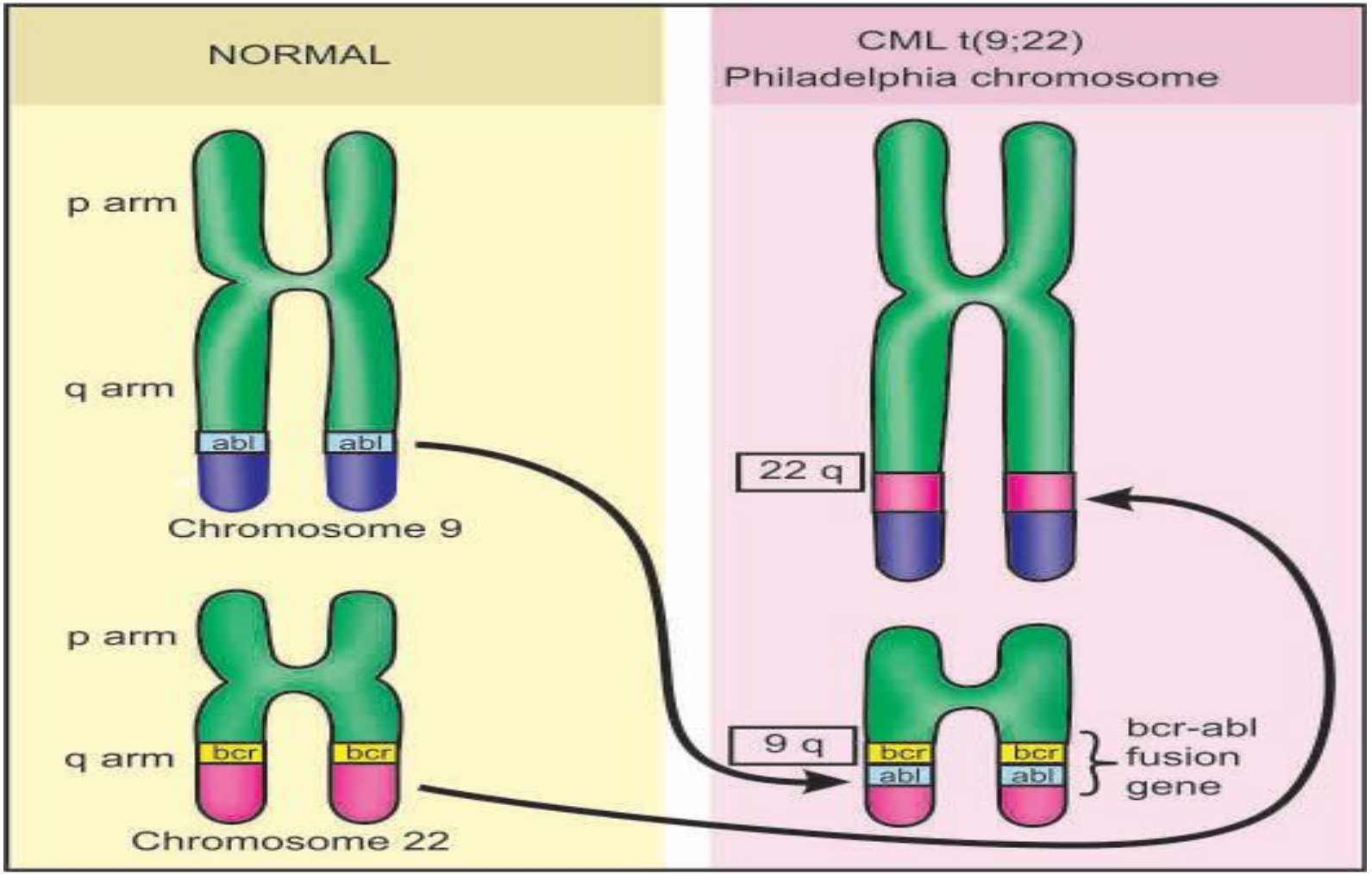
NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
22 q
p arm
q arm
bcr
bcr
Chromosome 22
9 q
bcr
bcr
abl
abl
bcr-abl
fusion
gene

IN TRANSLOCATION

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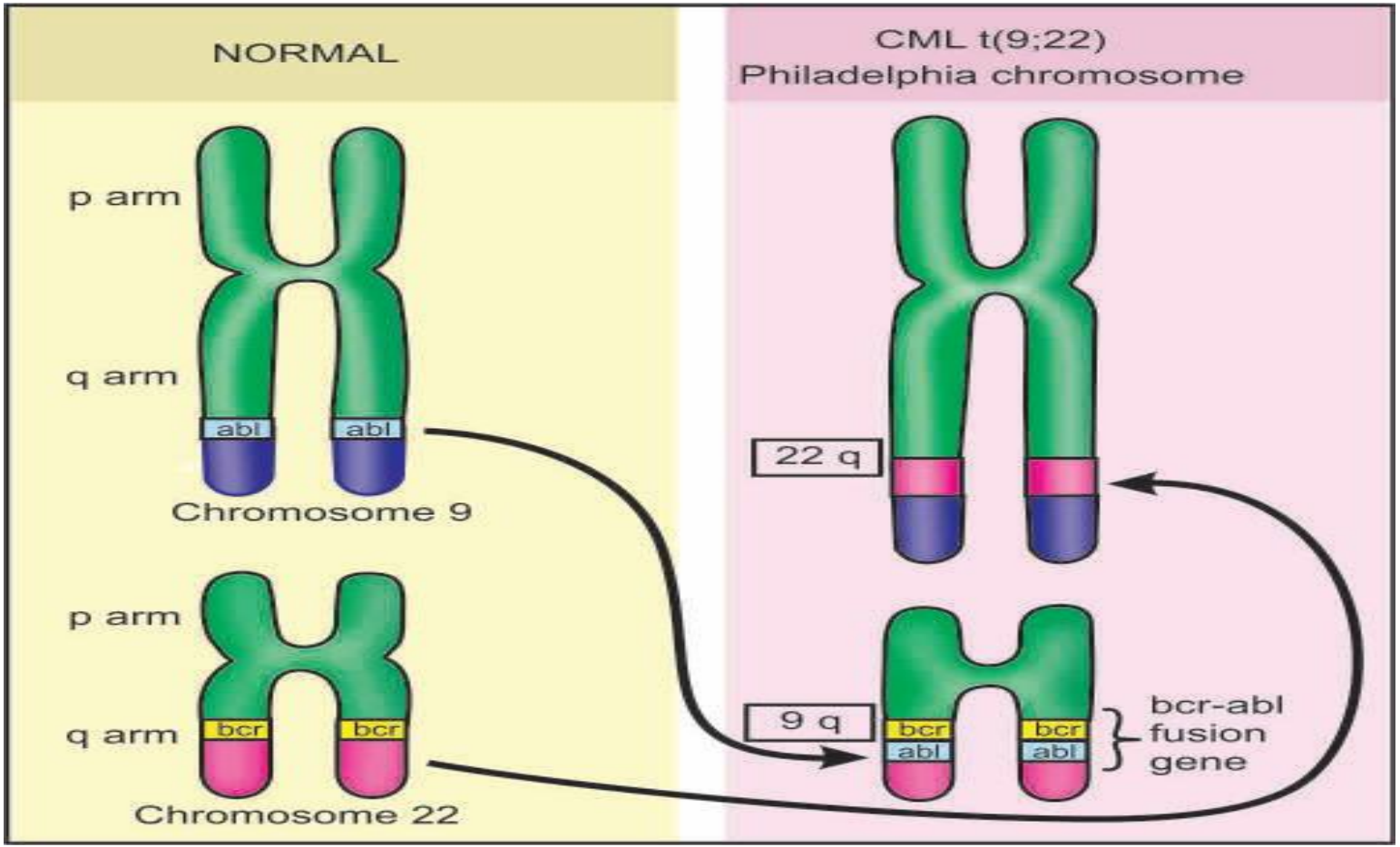
NORMAL
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Philadelphia chromosome
p arm
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abl
Chromosome 9
22 q
p arm
q arm
bcr
bcr
Chromosome 22
9 q
bcr
bcr
abl
abl
bcr-abl
fusion
gene

ABL gene → normal location on chromosome 9

↓

It is translocated to chromosome 22

↓

It fuses with BCR gene (breakpoint cluster region)

↓

Forms an ABL-BCR hybrid gene → Philadelphia chromosome on chromosome 22

↓

This hybrid do an abnormal signal transduction even without growth factors

↓

Uncontrolled mitosis

↓

Cancer

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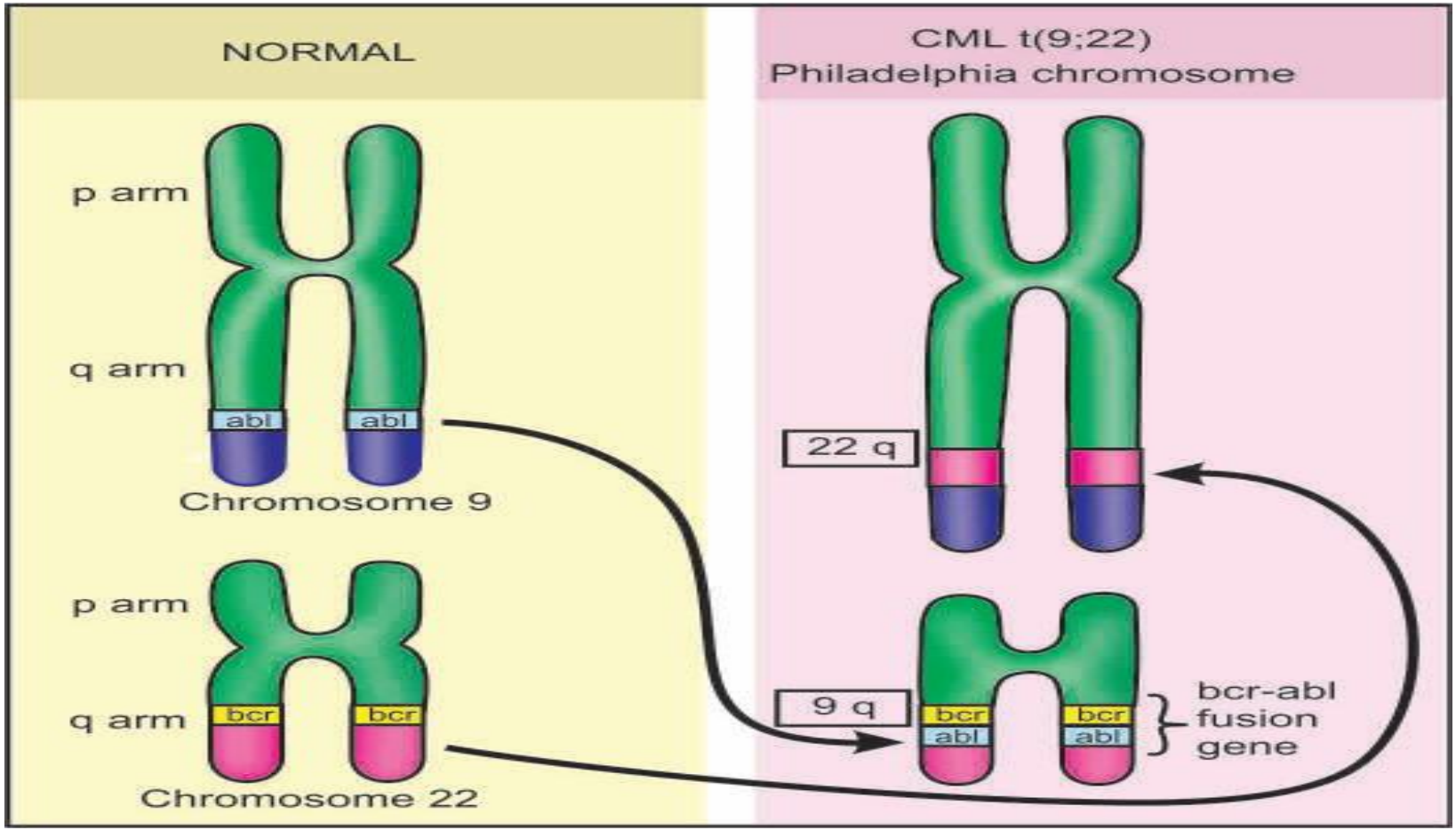
NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
22 q
p arm
q arm
bcr
bcr
Chromosome 22
9 q
bcr
abl
bcr
abl
bcr-abl
fusion
gene

EXAMPLE

- **CML**

- Now a days a specific tyosine kinase inhibitor drug called **imatinib** is used in treatment of CML
- This is an example of targeted drug therapy

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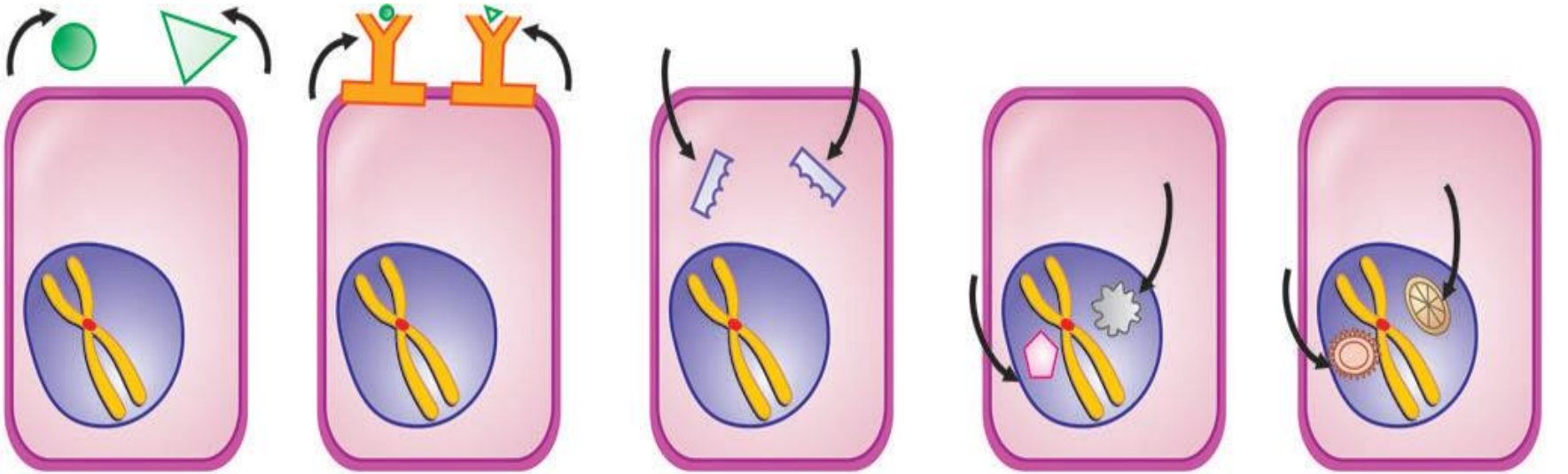

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MYC

- **MYC gene is a protooncogene having** nuclear regulatory activity (transcriptional activators).

- These are involved in carcinogenesis of many cancers

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C-MYC(NEET)	**Translocation**(PGI 06)	**Burkitt's lymphoma**(PGI 06)
N-MYC	**Amplification**(NEET)	**Neutoblastoma**(NEET)
L-MYC	Amplification	Lung carcinoma (small cell)

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NORMALLY

- MYC gene → normal location on chromosome 8

- IG gene→normal location on chromosome 14

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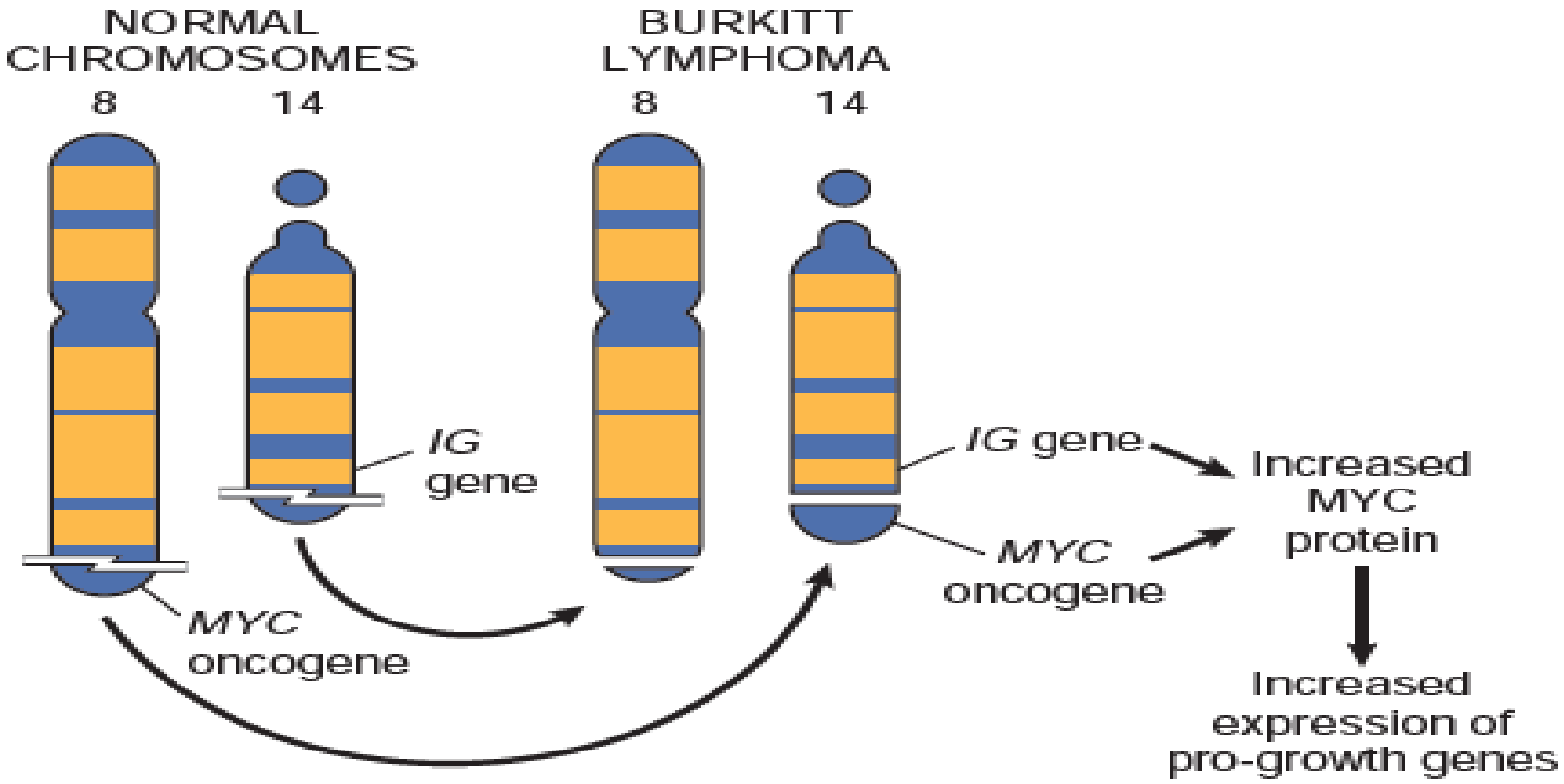

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IN TRANSLOCATION

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FOLLOW US
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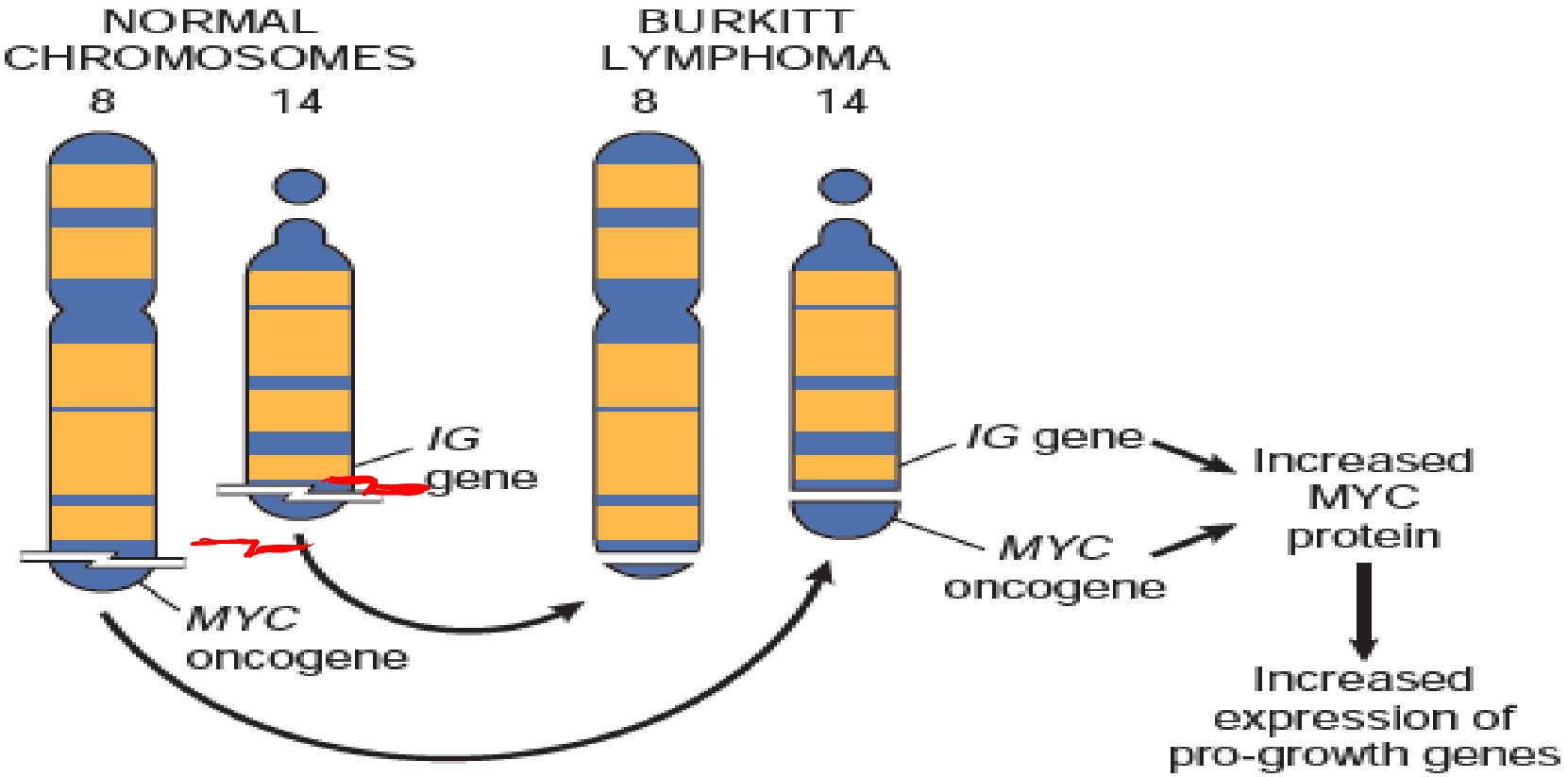

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MYC gene → normal location on chromosome 8

↓

It is translocated to chromosome 14

↓

It fuses with IG gene

↓

Forms an MYC-IG hybrid gene

↓

This hybrid has abnormal nuclear regulatory activity

↓

Uncontrolled mitosis

↓

Cancer

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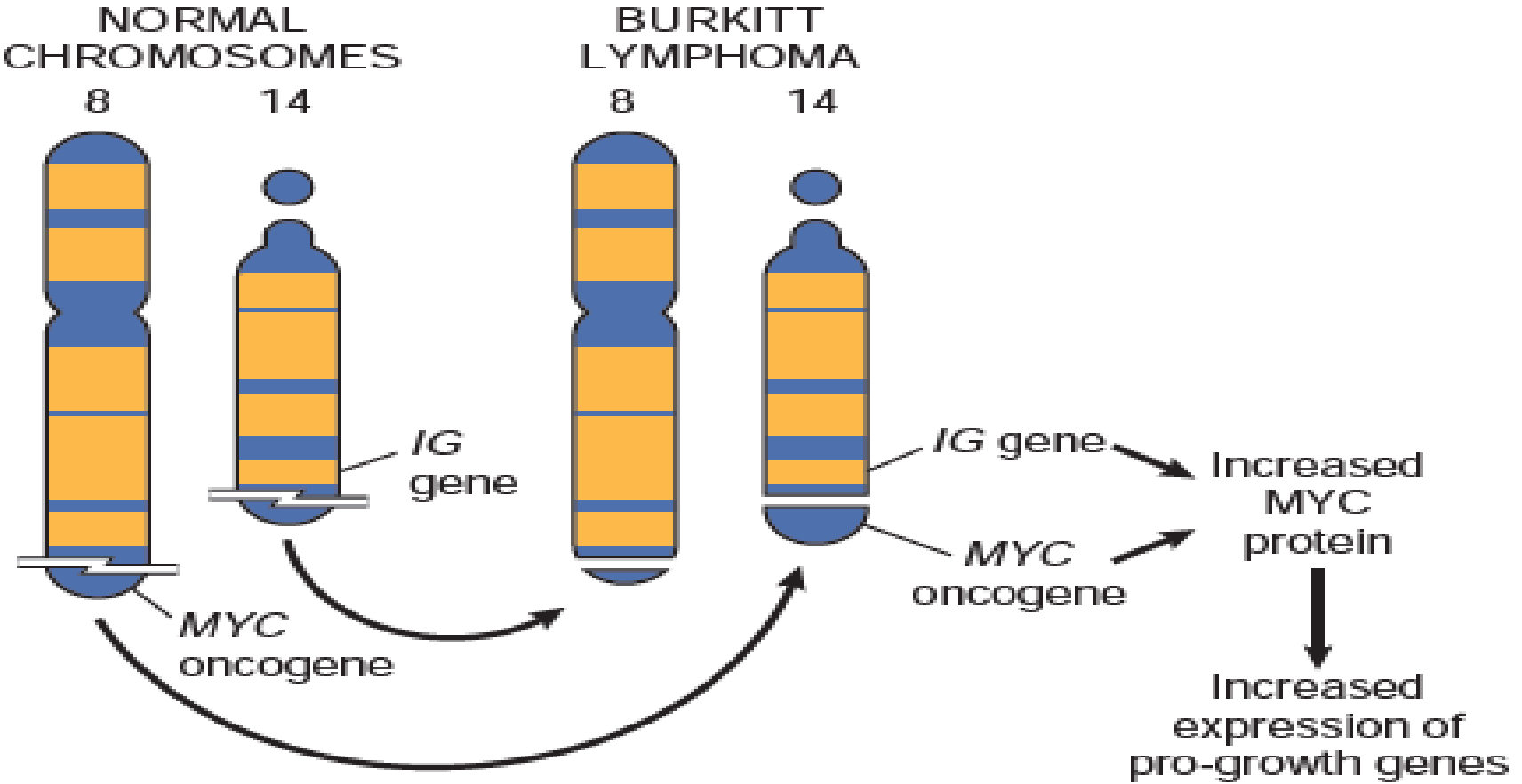
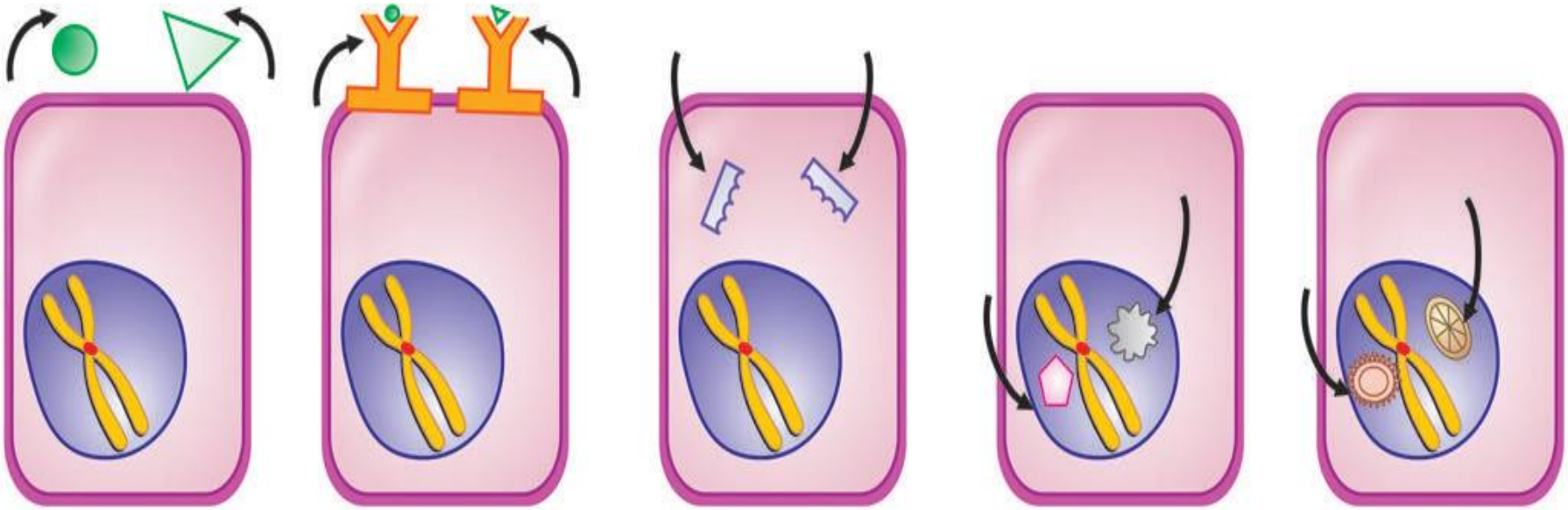

NORMAL CHROMOSOMES
8
14
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes



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POLLS 4

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The best example of a proto-oncogene activated by point mutation is -

a) Ras
b) N-myc
c) L-myc
d) Abl

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A

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Philadelphia chromosome is an example of-

a) Balanced translocation
b) Deletion
c) Non-dysjunction
d) Duplication

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A

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Amplification of N myc is associated with which tumour ?

a) Neuroblastoma
b) Retinoblastoma
c) Osteosarcoma
d) Neuroma

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A

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- C-MYC translocation causes Burkitt's lymphoma.
- L-MYC amplification causes small cell carcinoma of lung.
- N-MYC amplification causes Neuroblastoma.

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All are growth promoting oncogenes except -

- a) F GF
- b) TGF-a
- c) TGF-B
- d) PDGF

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c

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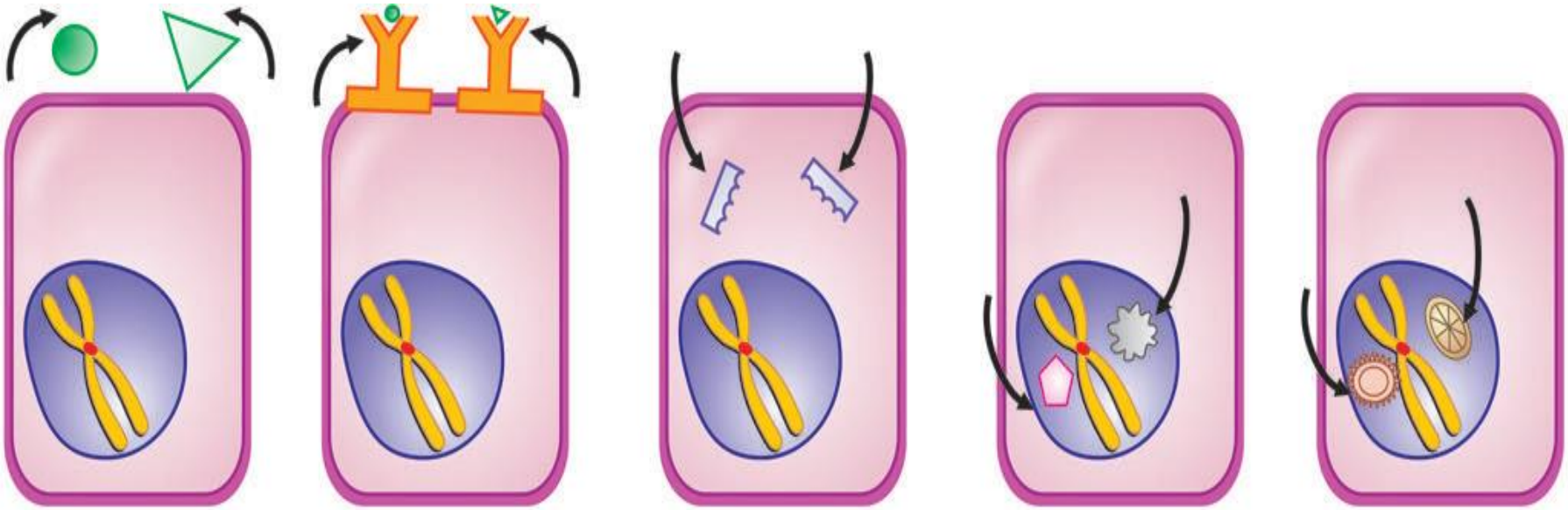

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MYC gene is -

- a) **Protein kinase inhibitor**
- **b) Growth factor inhibitor**
- **c) GTPase**
- **d) Transcription activator**

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D

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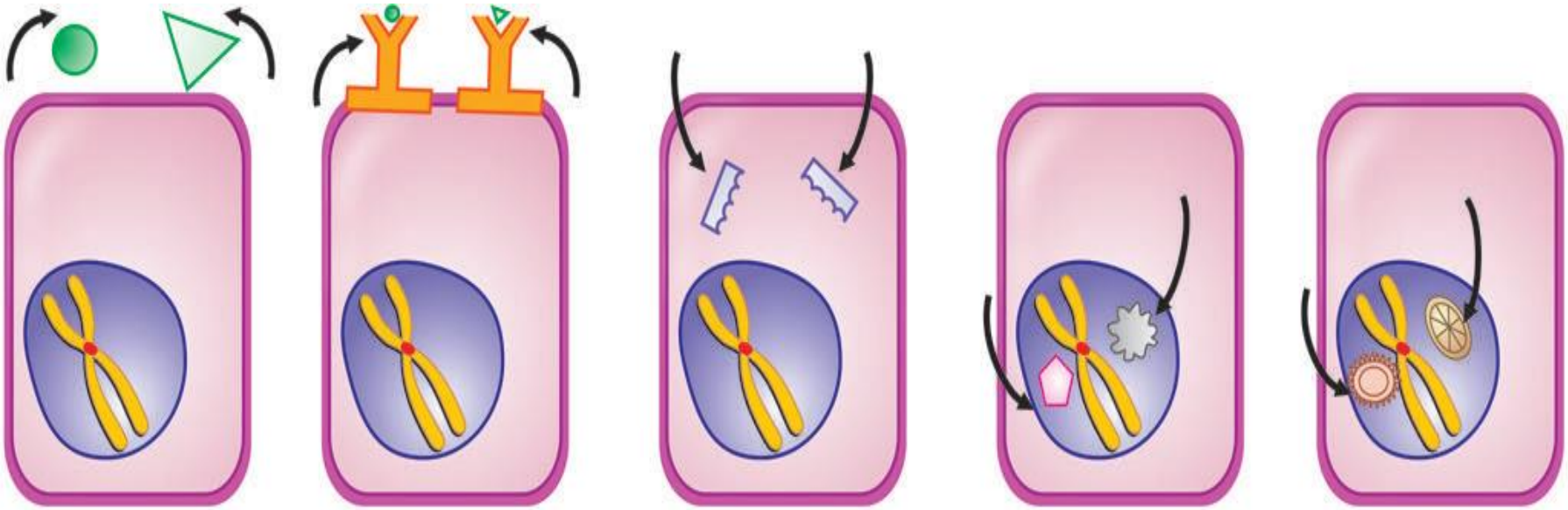

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Which of the following has tumor promoting effect?

- a) BRAC
- b) RB
- c) MYC
- d) p16

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c

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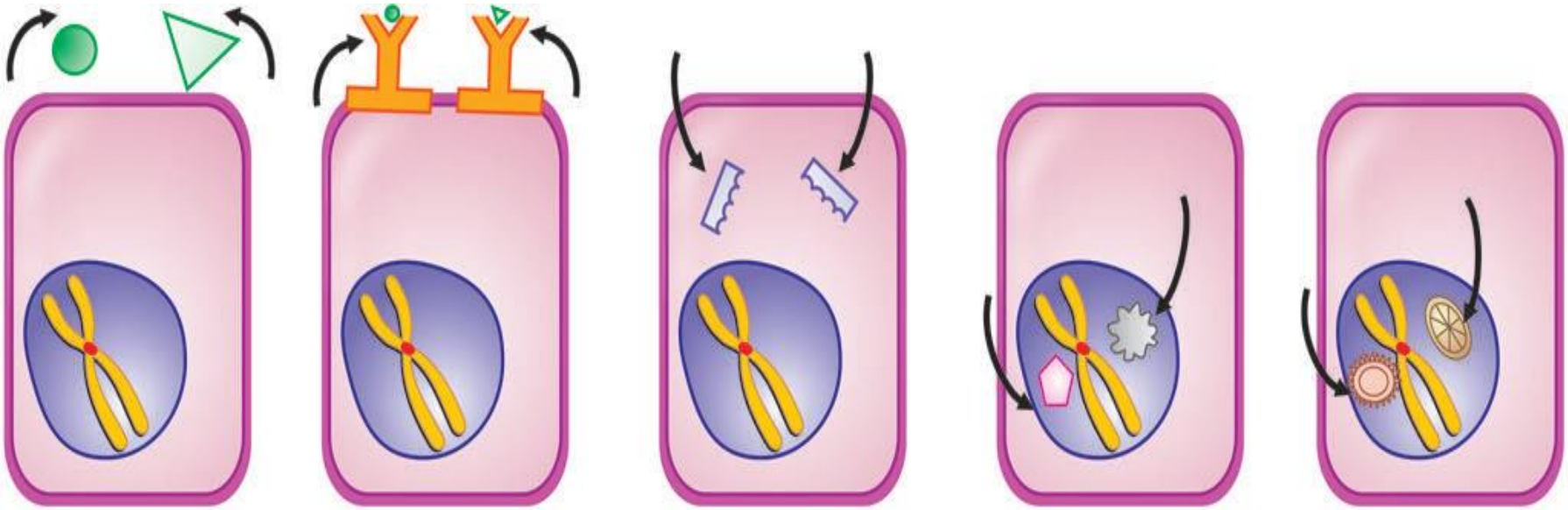

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In the MAPK pathway, the activation of RAS is counteracted by

a) Protein kinase C

b) GTPase activating protein

c) Phosphatidyl inositol

d) Inositol triphosphate

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B

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False about proto oncogenes

(a) Important for normal cell growth
(b) May get converted into oncogenes
(c) C-myc over-expression causes lymphon
(d) Their mutation causes retinoblastoma

D

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Following are required for normal growth exept

Following are required for normal growth:

(a) Proto-oncogenes
(b) Tumor suppressor genes
(c) Oncogenes
(d) DNA repair genes

c

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2. INACTIVATION OF Tumour sppressor genes

- Tumor suppressor genes are the genes whose products down regulate the cell cycle and **thus apply brakes to cellular proliferation**

- Normally tumour suppressor genes act by entering the cell into G0 (resting) phase

- So, **loss of function** of tumor suppressor genes results in uncontrolled cell proliferation and carcinogenesis.

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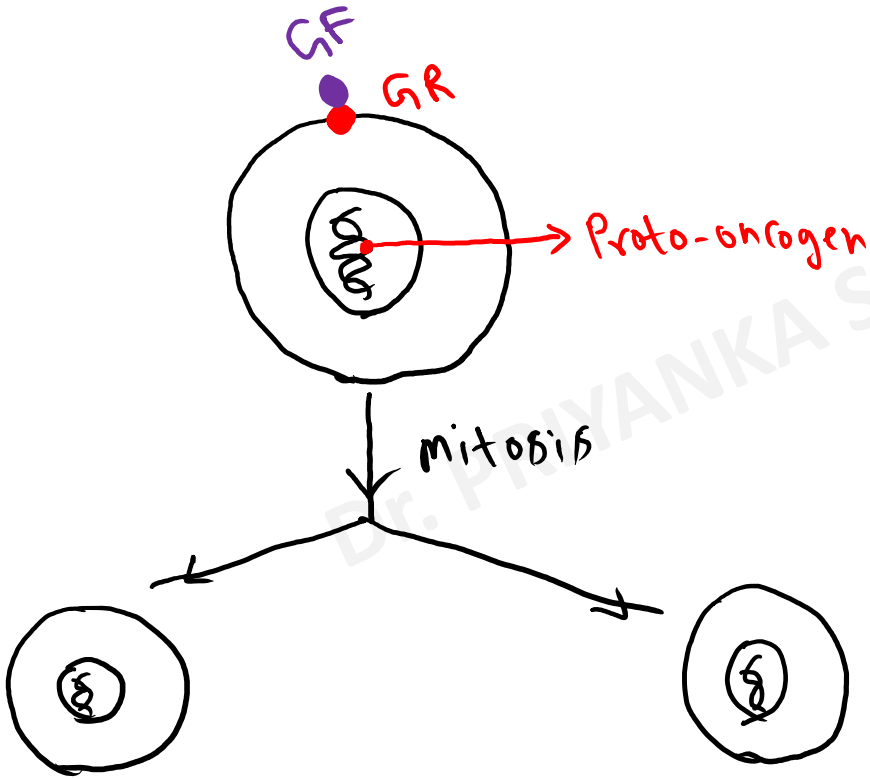
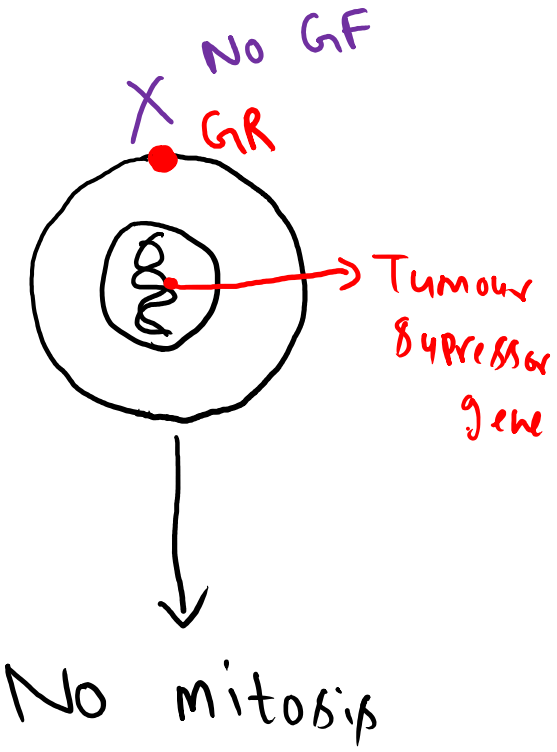
NORMAL CELL





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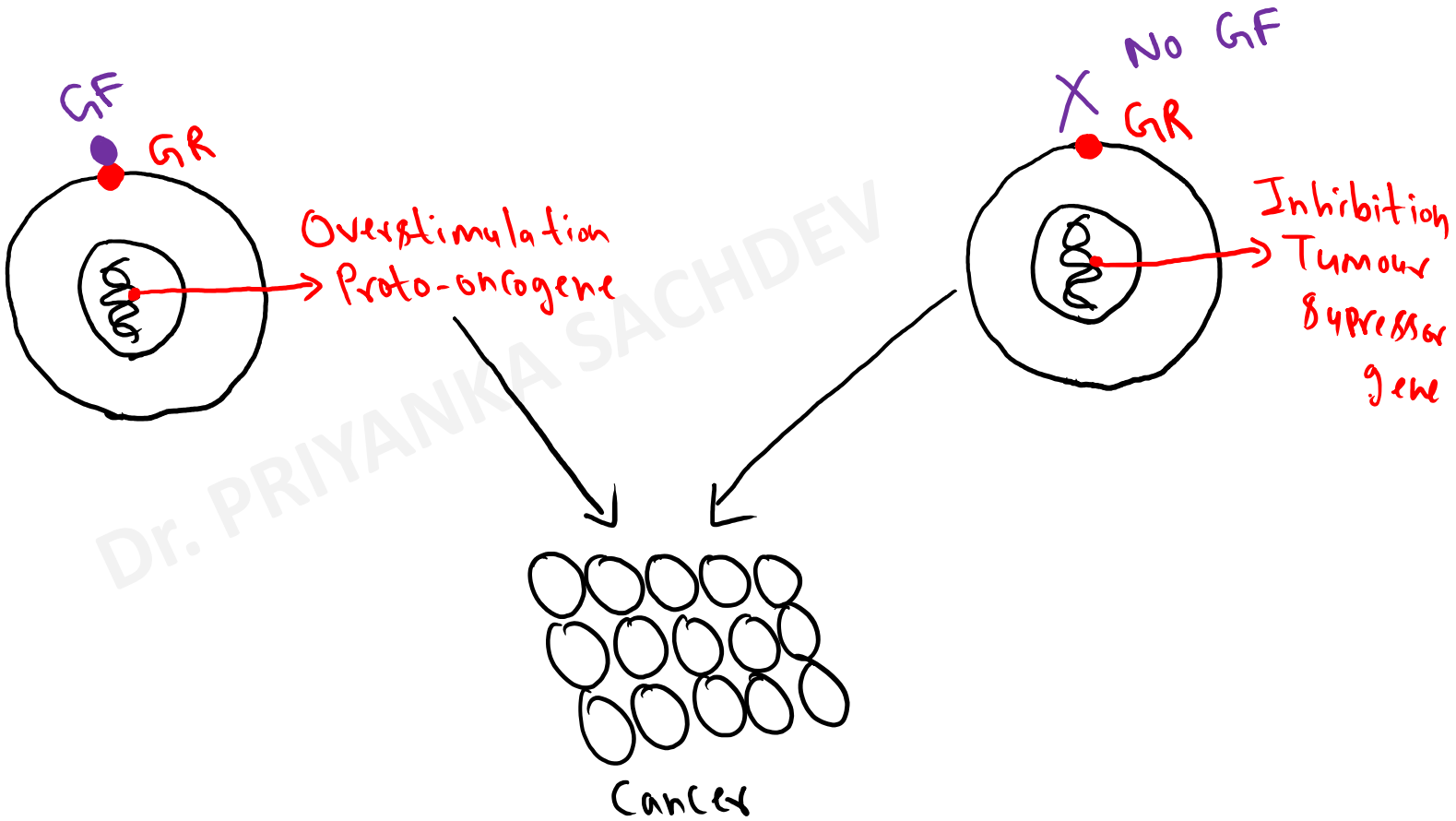
NORMAL CELL



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The mechanisms of loss of tumour suppressor actions of genes are due to

1.Chromosomal deletions

2. Point mutations

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CLASSIFICATION

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	GENE	LOCATION	ASSOCIATED HUMAN TUMOURS
1.	*RB*	Nucleus (13q)	Retinoblastoma, osteosarcoma
2.	*p53 (TP53)*	Nucleus (17p)	Most human cancers, common in Ca lung, head and neck, colon, breast
3.	*TGF–β and its receptor*	Extracellular	Ca pancreas, colon, stomach
4.	*APC and β-catenin proteins*	Nucleus, cytosol	Ca colon
5.	*Others*		
	i) BRCA 1 and 2	Nucleus (*BRCA1* 17q21, *BRCA2* 13q12-13)	Ca breast, ovary
	ii) VHL	Nucleus (3p)	Renal cell carcinoma
	iii) WT 1 and 2	Nucleus (11p)	Wilms' tumour
	iv) NF 1 and 2	Plasma membrane	Neurofibromatosis type 1 and 2

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RB gene

- Located on long arm (q) of **chromosome 13 (chromosome 13q14)**

- RB gene was the **first tumor suppressor gene to be discovered**

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NORMALLY

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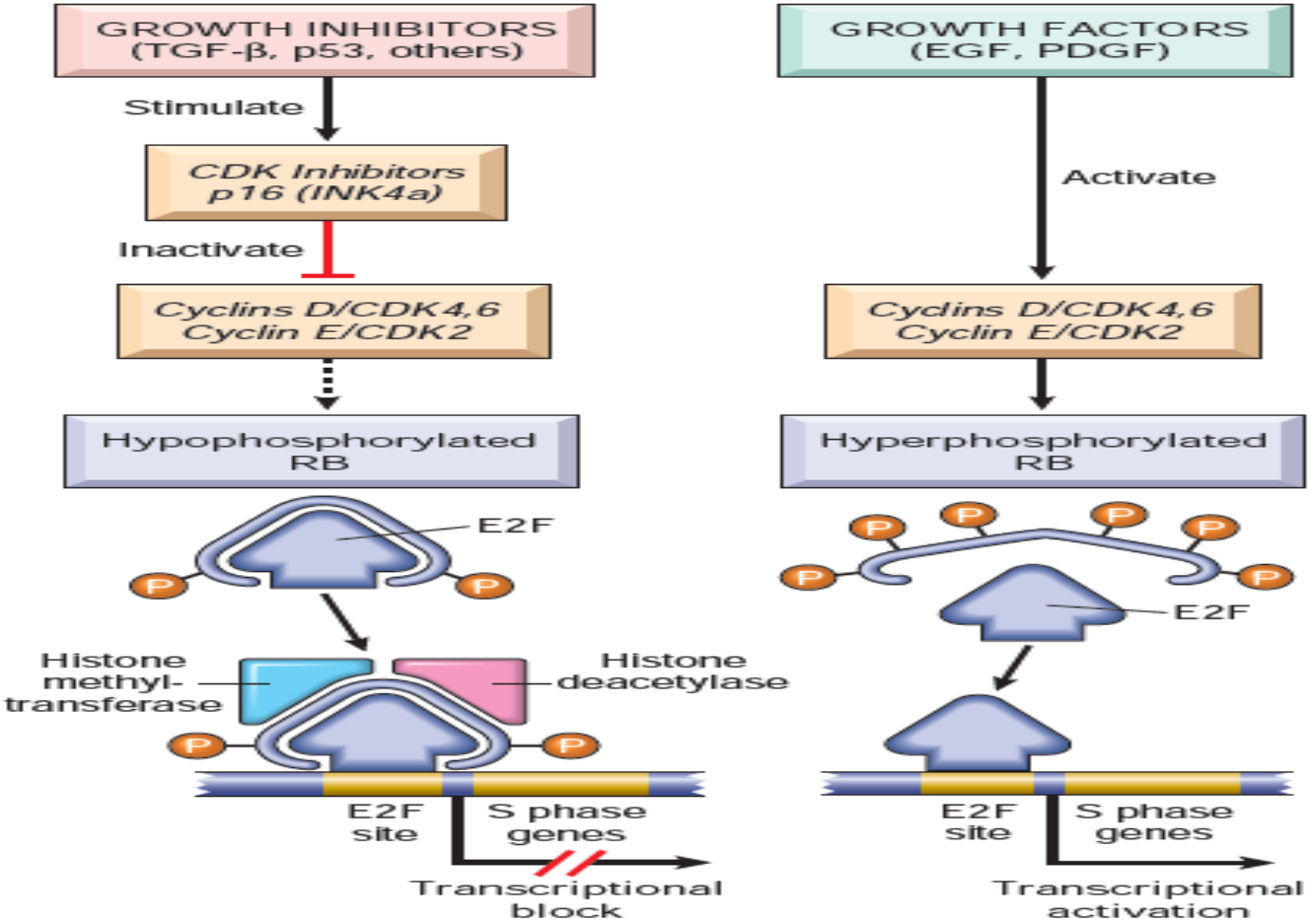
GROWTH INHIBITORS
(TGF-β, p53, others)
Stimulate
CDK Inhibitors
p16 (INK4a)
Inactivate
Cyclins D/CDK4,6
Cyclin E/CDK2
Hypophosphorylated
RB
E2F
P
Histone
methyl-
transferase
Histone
deacetylase
E2F
site
S phase
genes
Transcriptional
block
GROWTH FACTORS
(EGF, PDGF)
Activate
Cyclins D/CDK4,6
Cyclin E/CDK2
Hyperphosphorylated
RB
E2F
E2F
site
S phase
genes
Transcriptional
activation

Growth inhibitors

↓

Activates CDK inhibitors and inactivates cyclins and CDKS

↓

Hypophosphorylation of RB

↓

RB becomes active

↓

forming an inactive complex with transcription factor EF-2

↓

blocks cell division (no mitosis)

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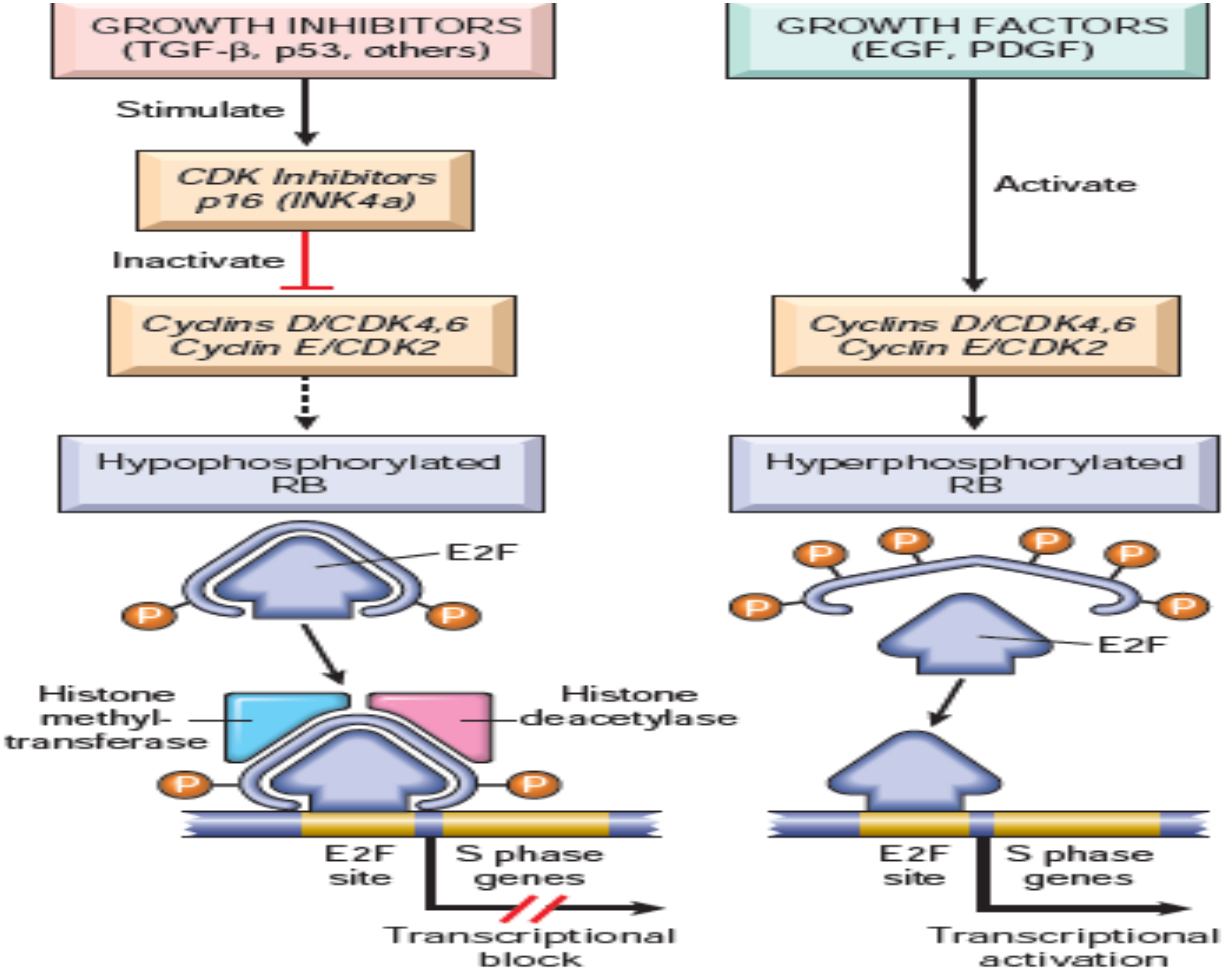
GROWTH INHIBITORS
(TGF-β, p53, others)
Stimulate
CDK Inhibitors
p16 (INK4a)
Inactivate
Cyclins D/CDK4,6
Cyclin E/CDK2
Hypophosphorylated
RB
E2F
P
Histone
methyl-
transferase
Histone
deacetylase
E2F
site
S phase
genes
Transcriptional
block
GROWTH FACTORS
(EGF, PDGF)
Activate
Cyclins D/CDK4,6
Cyclin E/CDK2
Hyperphosphorylated
RB
E2F
E2F
site
S phase
genes
Transcriptional
activation

Growth factors

↓

Activates cyclins and CDKS

↓

Hyperphosphorylation of RB

↓

RB becomes inactive

↓

Dislocation of RB from transcription factor EF-2

↓

Cell division (mitosis)

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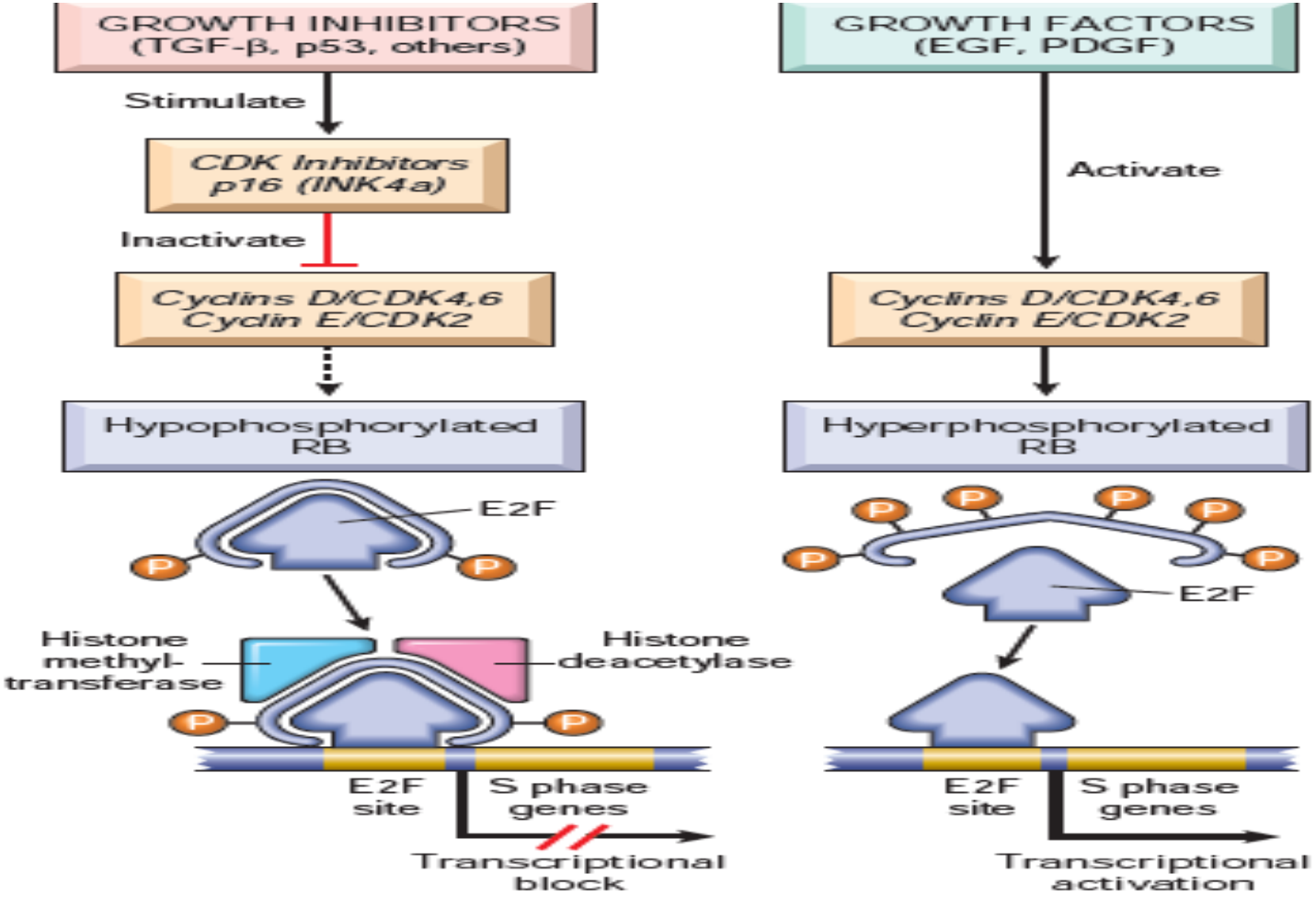

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Mutation in RB→

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Like us

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Mutation in RB

↓

Permanent inactivation of RB

↓

Permanent Dislocation of RB from transcription factor EF-2

↓

Abnormal Cell division (mitosis)

↓

Cancer

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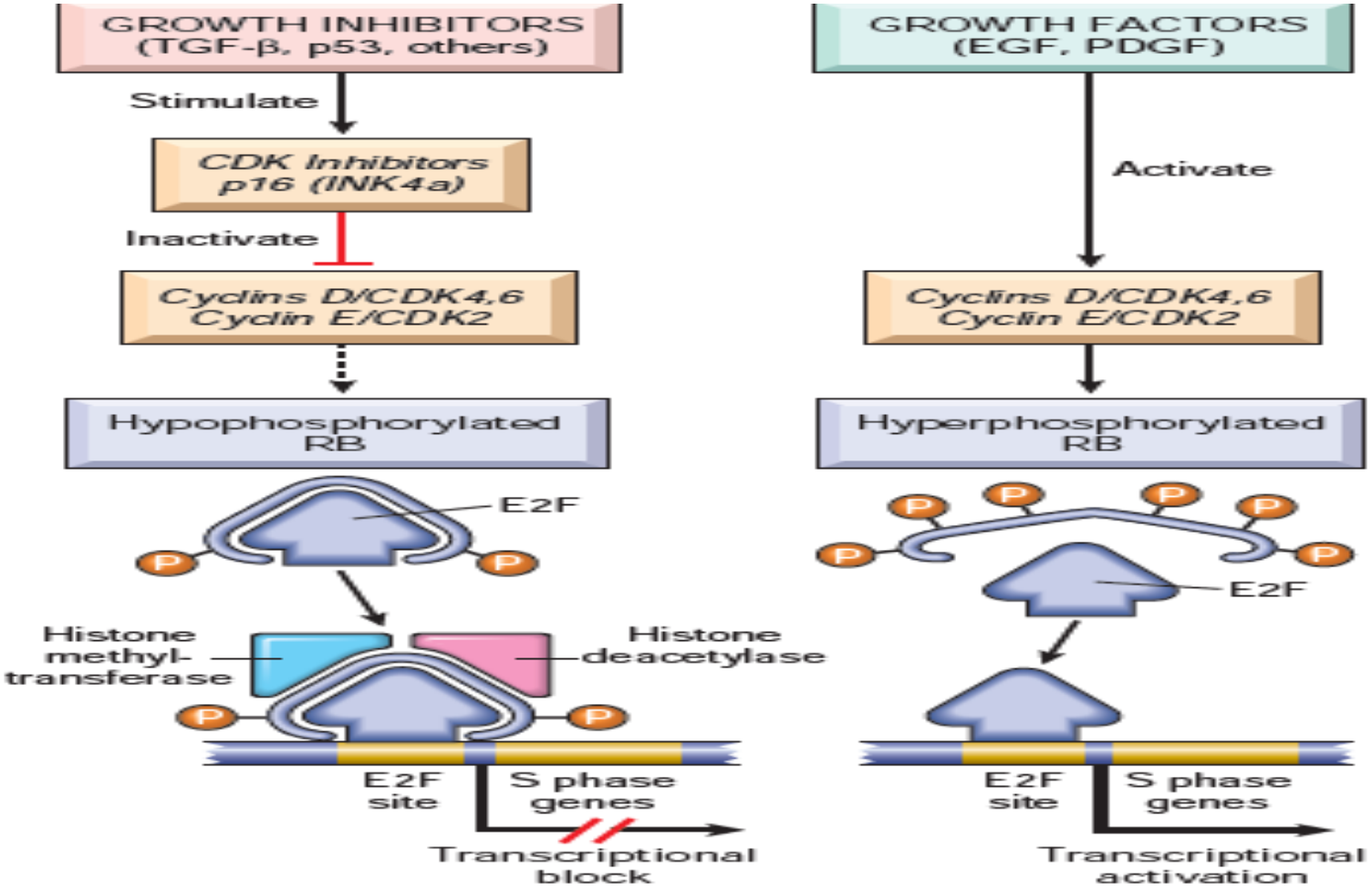

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ACTIVE RB gene →

- active in hypophosphorylated state
- prevents replication by forming an inactive complex with transcription factor EF-2.
- blocks cell division
- inhibiting the cell cycle at G1 → S phase

INACTIVE RB gene→

- Phosphorylation of RB gene causes inactivation of RB gene
- dissociation of RB from EF-2.
- activation of EF-2
- cell replication.

Mutation in RB→

Permanent **inactivation** of RB

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- Retinoblastoma is associated with concept of

1. **Loss of Heterozygosity**
2. **Knudson's Two Hit Hypothesis**

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Knudson's two hit hypothesis→

- Retinoblastoma develops when both the normal alleles of the RB genes are inactived

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Familial/Hereditary retinoblastoma

- First genetic change (first hit) in RB gene is inherited from an affected parent

- second mutation (second hit) occurs in postnatal life and both alleles are lost.

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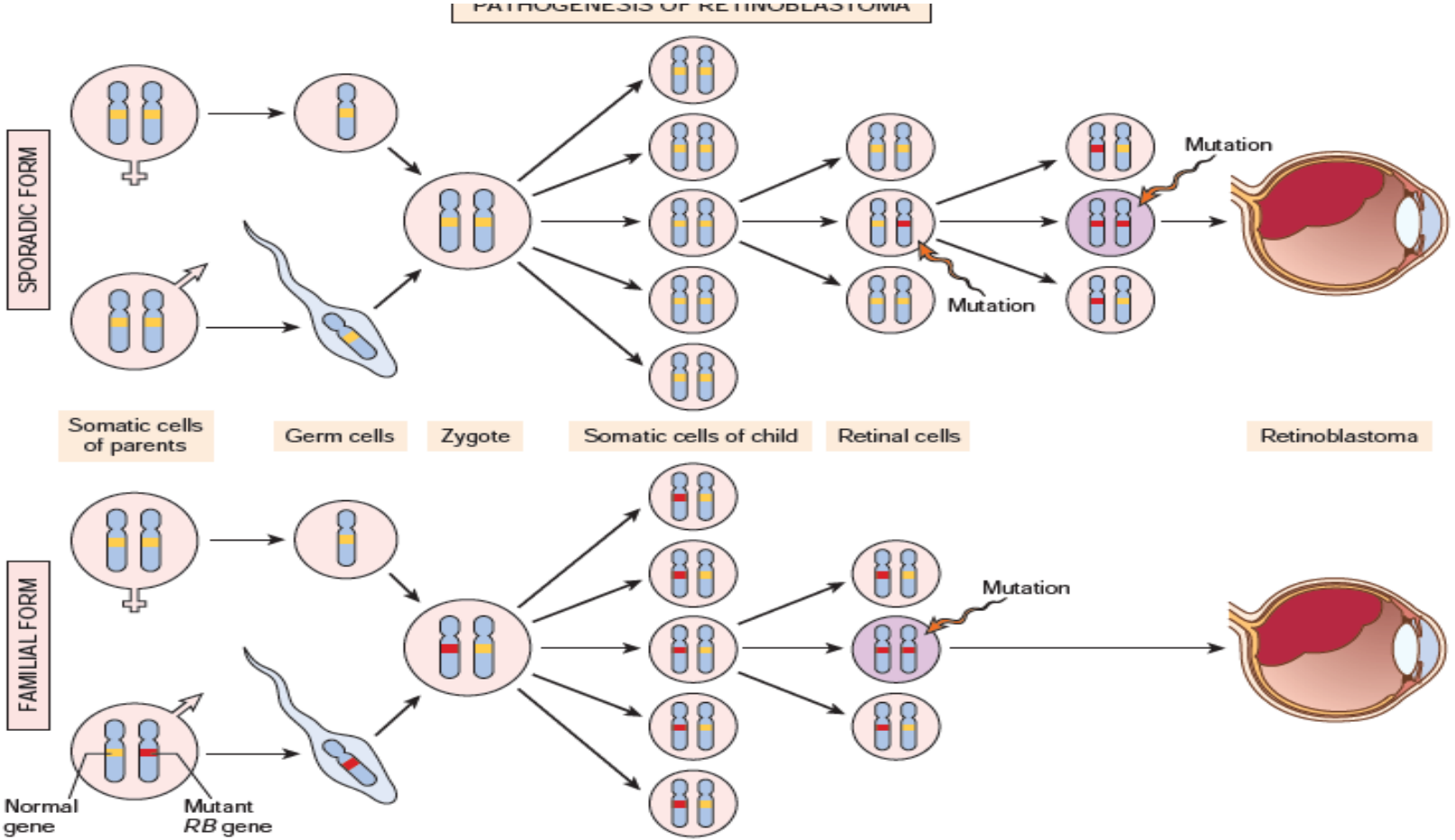
PATHOGENESIS OF RETINOBLASTOMA
SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant RB gene

- In hereditary retinoblastoma, children are born with one normal and one abnormal RB gene, i.e. **Heterozygous for RB gene.**

- Mutation in normal RB gene results in loss of heterozygosity (as both RB genes become abnormal) and development of retinoblastoma→ **Loss of Heterozygosity**

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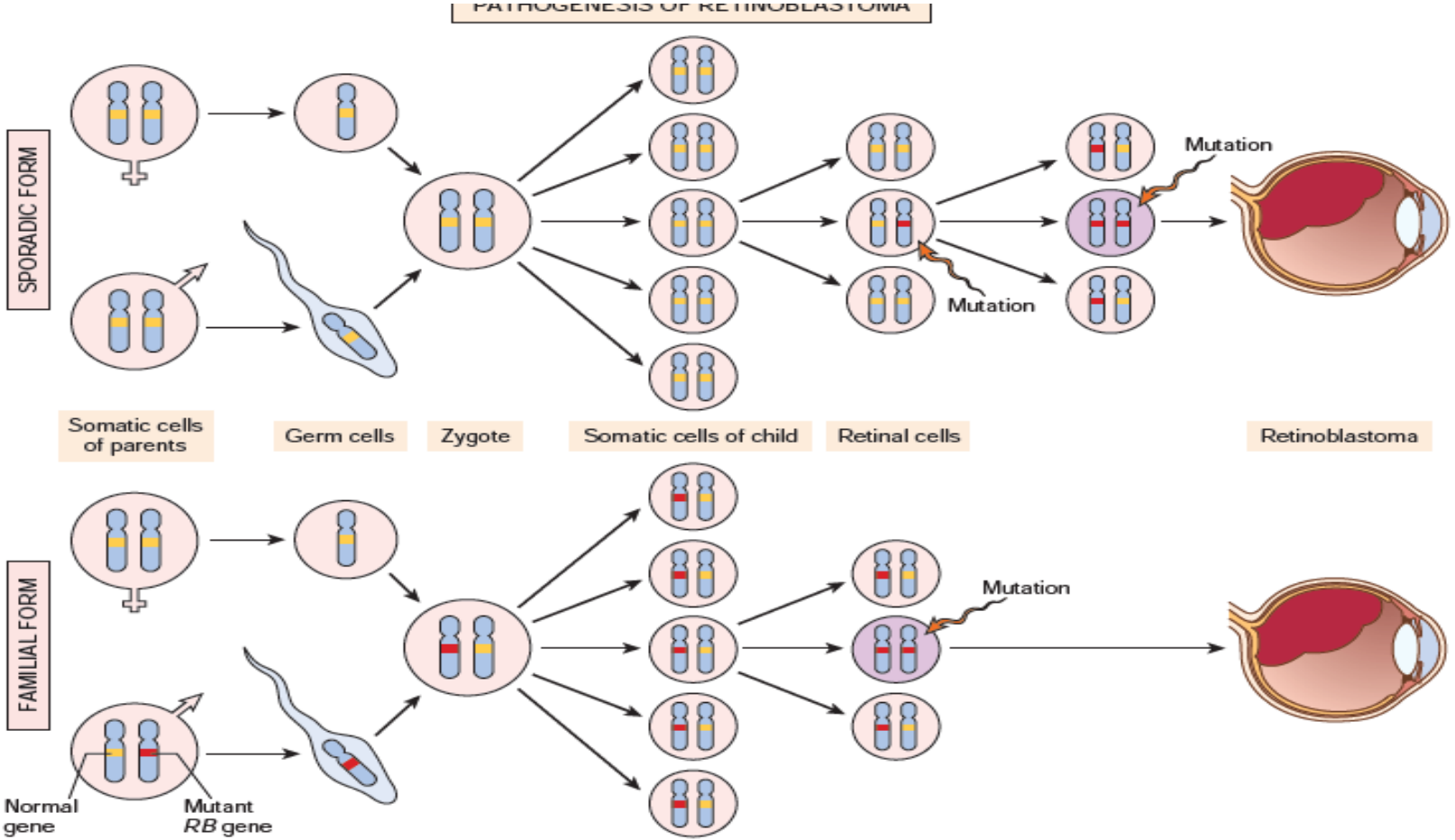
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SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
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Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant RB gene

Sporadic/non- hereditary retinoblastoma

- Both mutations (first and second hits) occur postnataly.

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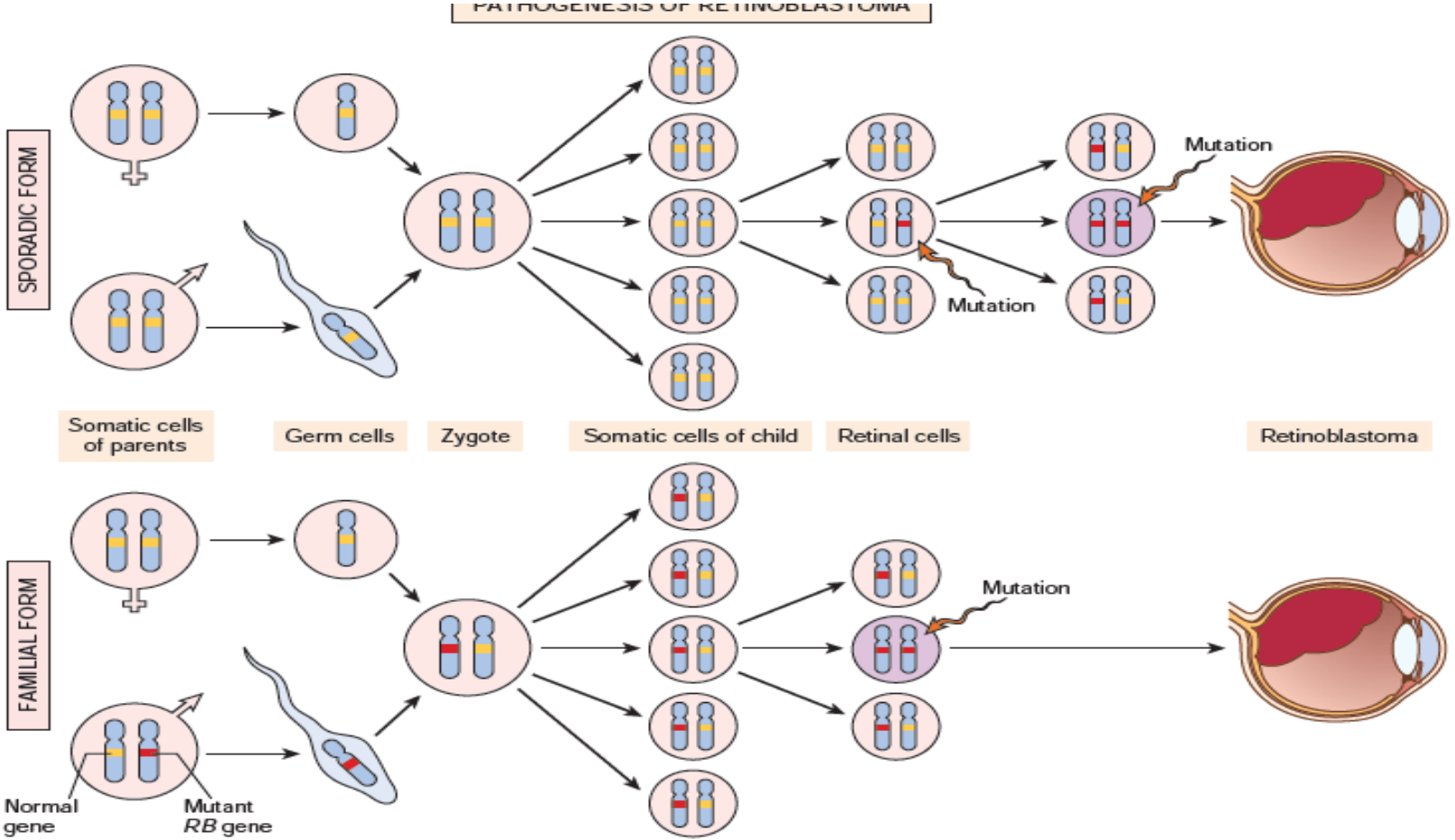
PATHOGENESIS OF RETINOBLASTOMA
SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant RB gene

Familial retinoblastoma

- comprises 40% of cases
- bilateral.
- **somatic cells inherit one mutant RB gene from a carrier parent (i.e. germline mutation). The other mutation occurs after birth.**
- Besides retinoblastoma, children inheriting mutant RB gene have **200 times greater risk of development of other cancers eg osteosarcoma, breast, colon and lungs.**

Sporadic retinoblastoma

- constitutes 60% of cases
- unilateral.
- **acquired both the somatic mutations in the two alleles after birth.**

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- **Familial Retinoblastoma is also associated with increased risk of osteosarcomas.**

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REMEMBER

- **Retinoblastoma is associated with Concept of Loss of Heterozygosity as well as Knudson's Two Hit Hypothesis**

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	GENE	LOCATION	ASSOCIATED HUMAN TUMOURS
1.	*RB*	Nucleus (13q)	Retinoblastoma, osteosarcoma
2.	*p53 (TP53)*	Nucleus (17p)	Most human cancers, common in Ca lung, head and neck, colon, breast
3.	*TGF–β and its receptor*	Extracellular	Ca pancreas, colon, stomach
4.	*APC and β-catenin proteins*	Nucleus, cytosol	Ca colon
5.	*Others*		
	i) BRCA 1 and 2	Nucleus (*BRCA1* 17q21, *BRCA2* 13q12-13)	Ca breast, ovary
	ii) VHL	Nucleus (3p)	Renal cell carcinoma
	iii) WT 1 and 2	Nucleus (11p)	Wilms' tumour
	iv) NF 1 and 2	Plasma membrane	Neurofibromatosis type 1 and 2

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P53 gene

- p53 is a **tumor suppressor gene.**
- p53 gene is located on **chromosome 17**
- **Guardian of genome**
- **Molecular policeman**

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- **P53 is a tumour suppressor gene as well as DNA repair gene**

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In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

iv) Inactivation of DNA repair genes

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NORMALLY

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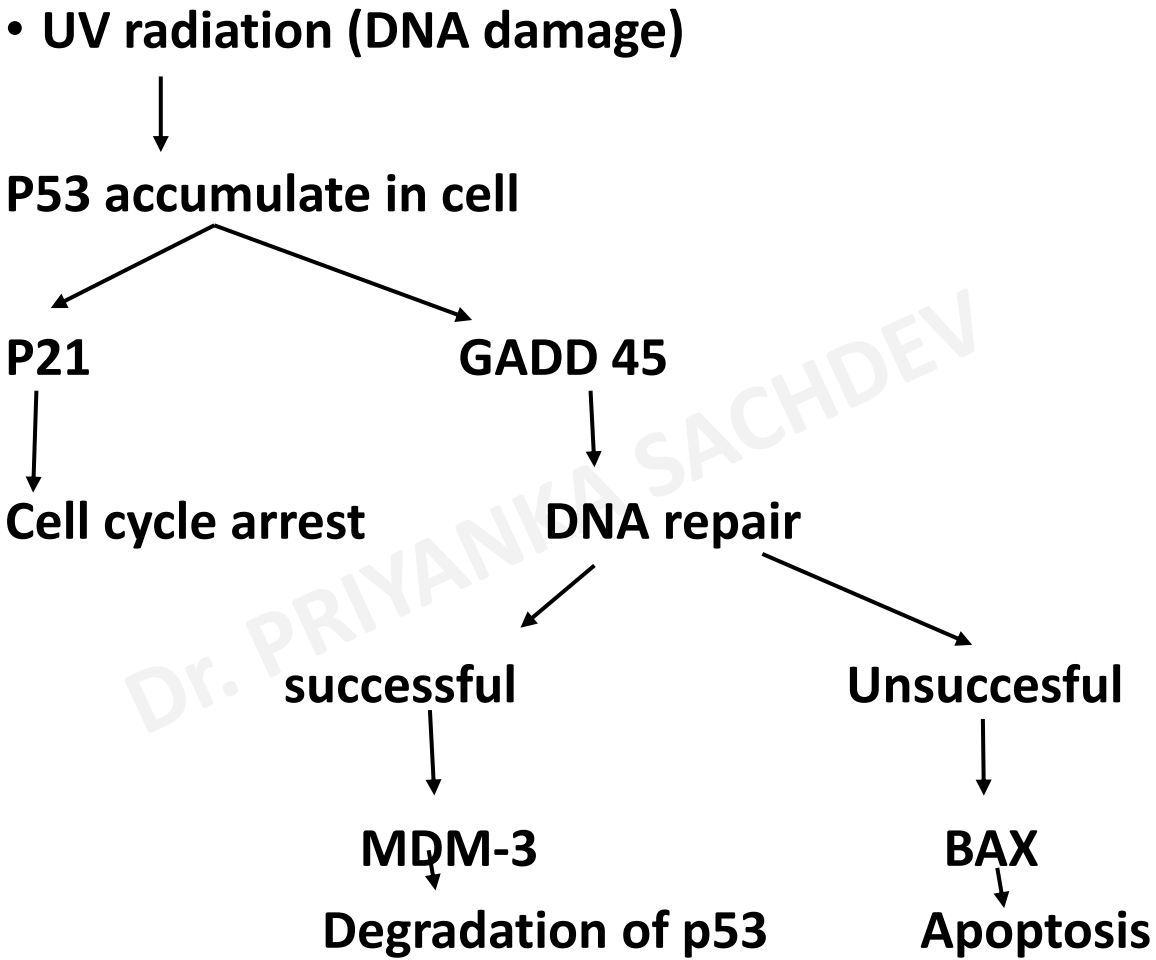

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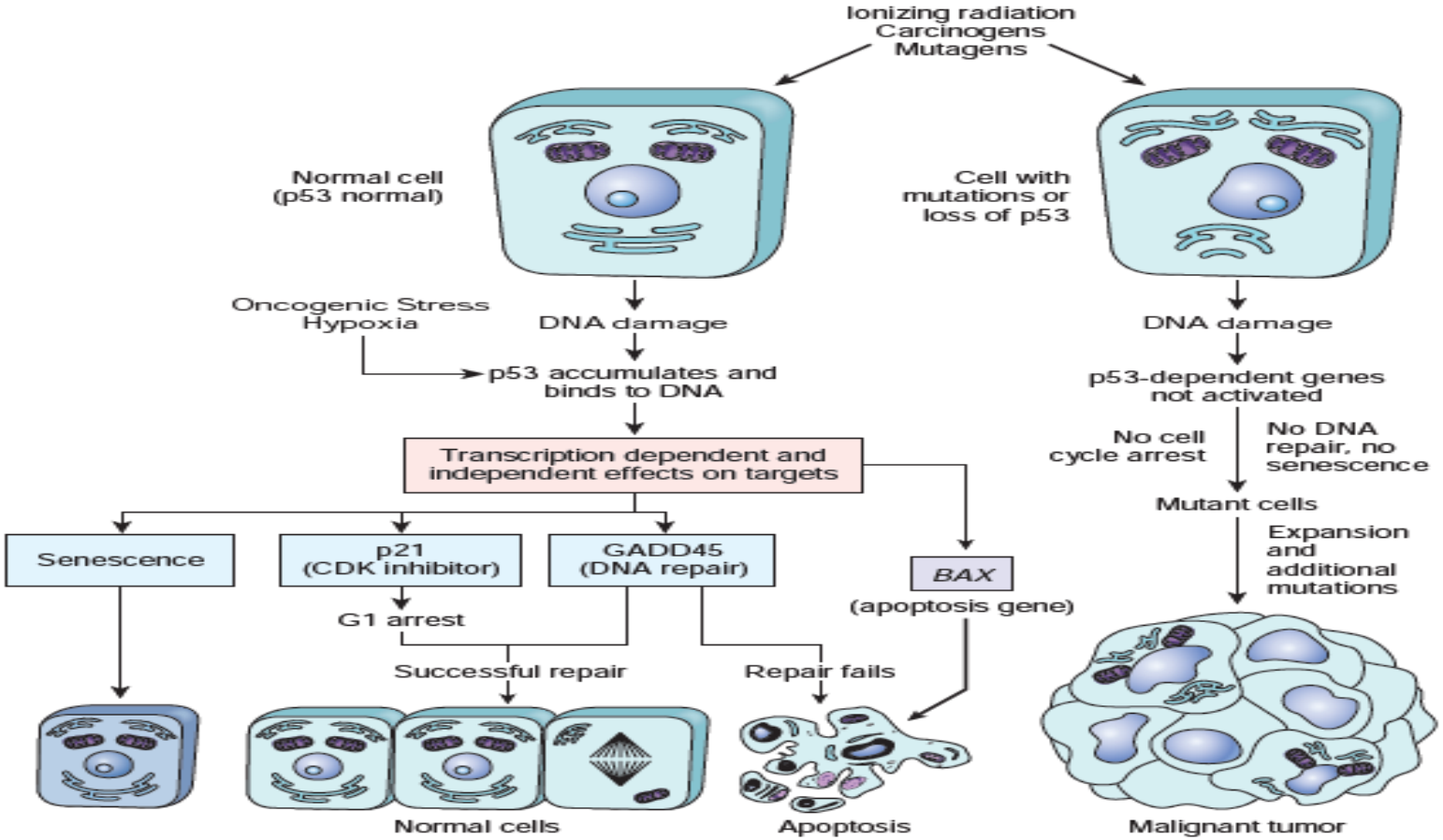
Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Oncogenic Stress
Hypoxia
DNA damage
DNA damage
p53 accumulates and
binds to DNA
p53-dependent genes
not activated
No cell
cycle arrest
No DNA
repair, no
senescence
Transcription dependent and
independent effects on targets
Mutant cells
Expansion
and
additional
mutations
Senescence
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

- **p53 acts through: CDK inhibitor p21**
- p53 itself is not a CDK inhbitor

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Mutation in p53

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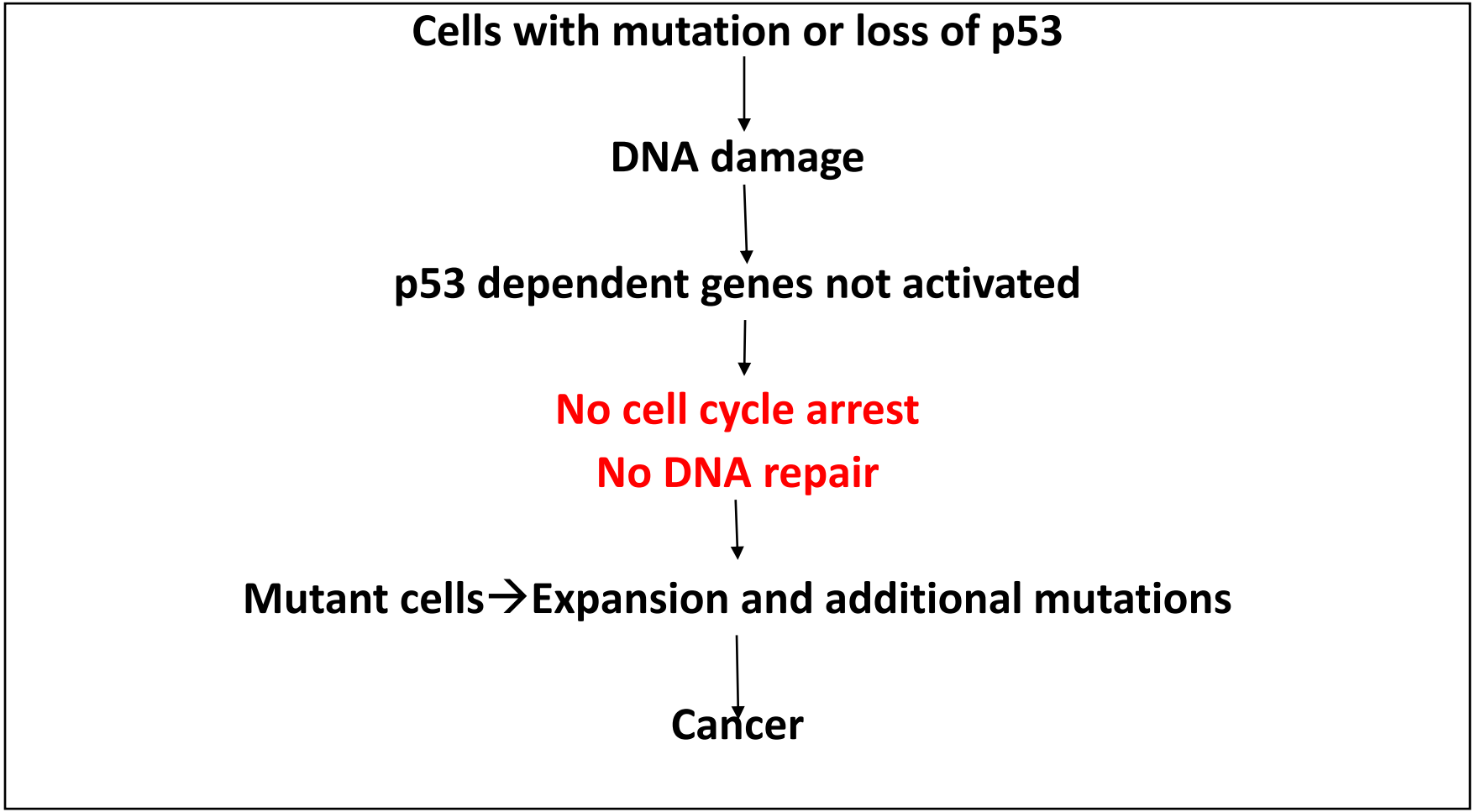
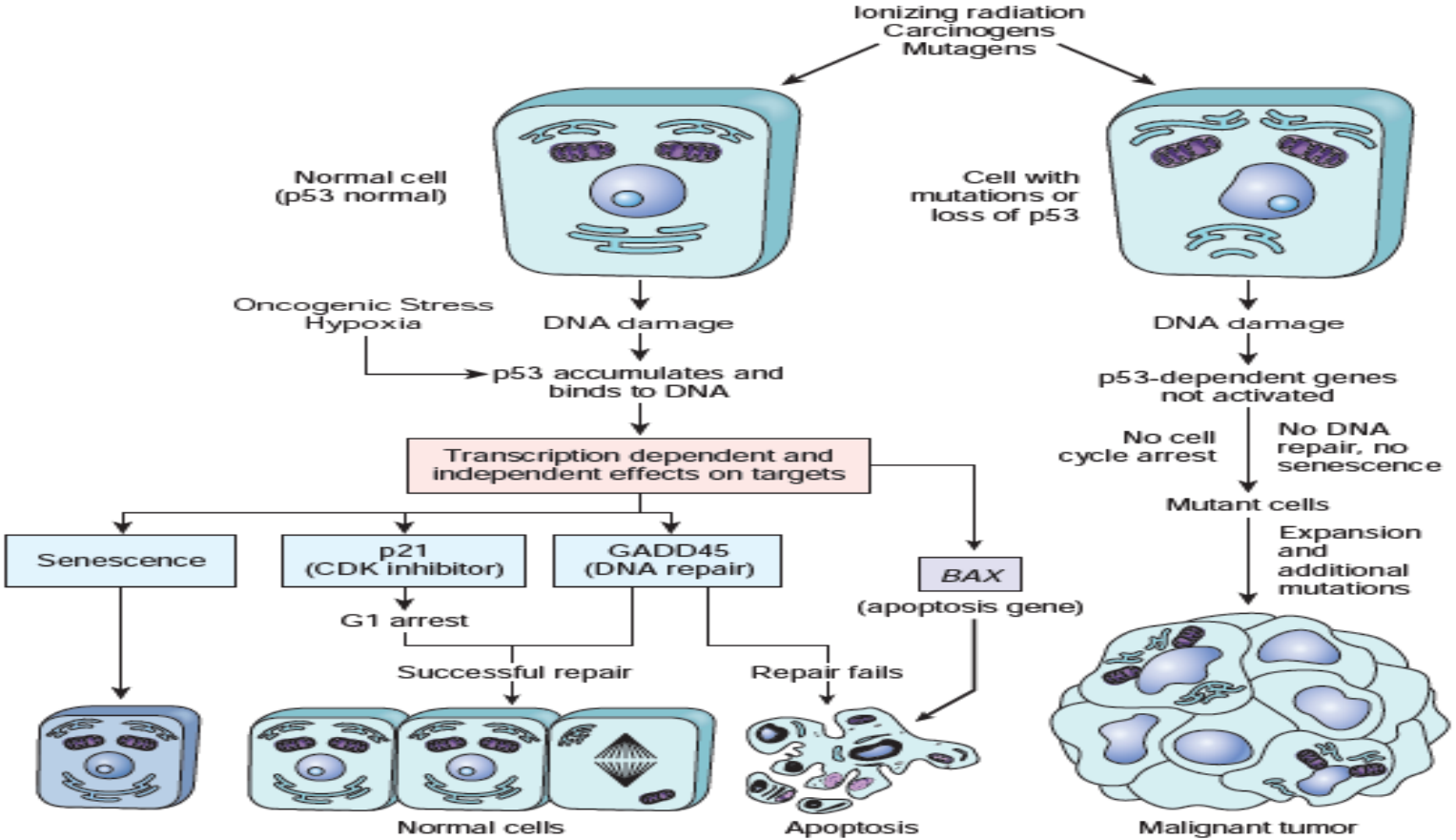

Cells with mutation or loss of p53
DNA damage
p53 dependent genes not activated
No cell cycle arrest
No DNA repair
Mutant cells→Expansion and additional mutations
Cancer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p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

- When there is DNA damage due to irradiation, UV light or mutagenic chemicals, there is rapid increase in p53 levels.
- p53 causes→

i) Cell cycle arrest:

- p-53 induces transcription of p21, a CDK inhibitor.
- p21 inhibit cyclin D-CDK-4 complex
- arrest of cell cycle in G1 phase.
- This allow time for DNA repair.

ii) DNA repair:

- inducing transcription of GADD 45 (growth arrest and DNA damage).
- GADD 45 encodes a protein that is involved in DNA repair.

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If DNA damage is repaired successfully,

- p53 activate MDM-3
- MDM-3 induce degradation of p-53→ Relieve in cell cycle block

If DNA damage cannot be successfully repaired,

- p53 induces apoptosis by inducing the activation of apoptosis inducing gene BAX
- So p-53 prevents replication of cell with defective DNA

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REMEMBER

- **Non-mutated (wild type)** p53 reduces the chances of cancer.

- **Mutated form** is associated with cancer

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- Sometimes individual may inherit one mutant p53 allele and the second acquired 'hit' may inactivate the normal p53 allele.

- This later condition is called **Li-Fraumeni syndrome**

- Associated with development of **sarcoma, breast cancer, leukemia and brain tumors.**

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- **Human papilloma virus (HPV)** causes inactivation of p53 through its **E6 protein**

- so,it is responsible for development of cancer of anal and genital region.

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- p73 (big brother of p53) and p63 are other members of the family of p53 gene.

- **p63** is esential for the **differentiation of stratified squamous epithelia.**

- **p73** has **pro-apoptotic effects after DNA damage induced by the chemotherapeutic agents**

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REMEMBER

- **Overall → p-53**
- Amongst **Tumour suppressor genes** → **p-53** is involved most commonly
- Amongst **Proto-oncogene** → **RAS** is involved most commonly

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POLLS 5

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An example of a tumour suppressor gene is -

- a) myc
- b) EGFR
- c) ras
- d) Rb

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D

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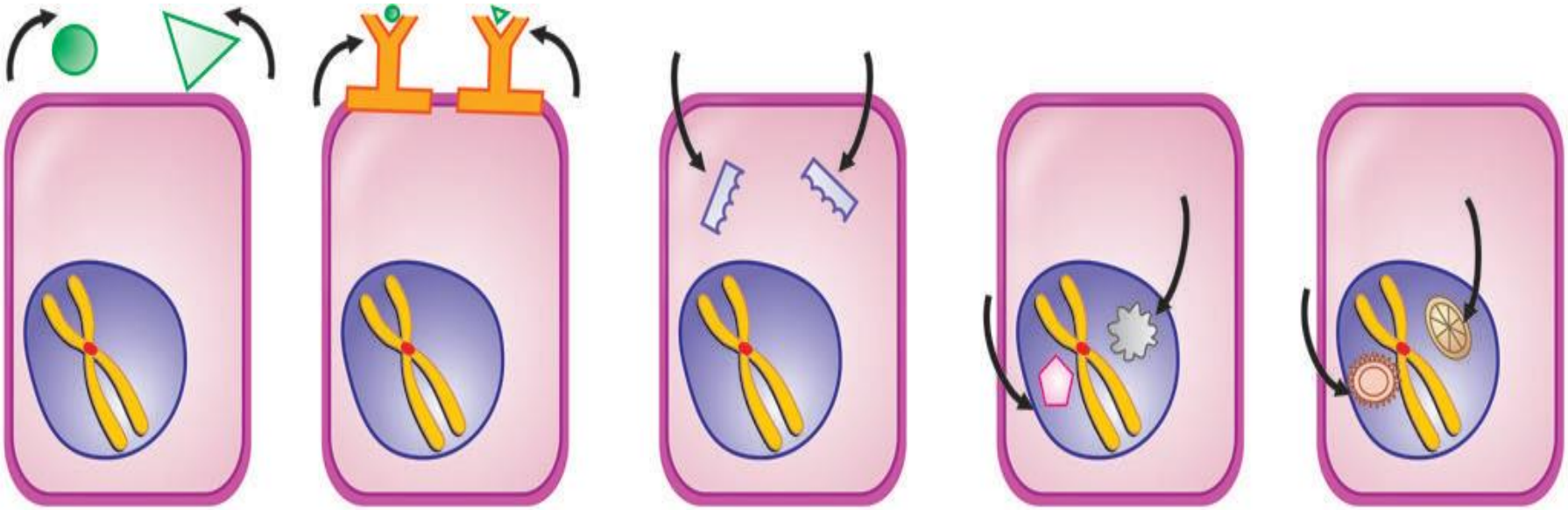

GROWTH FACTORS	RECEPTORS FOR GFs	CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS	NUCLEAR TRANSCRIPTION FACTORS	CELL CYCLE REGULATORY PROTEINS
i) PDGF-β ii) TGF-α iii) FGF iv) c-MET	i) EGF-R ii) c-KIT -R iii) RET-R iv) FMS-like	I) Mutated RAS ii) ABL-BCR	i) C-MYC ii) N-MYC iii) L-MYC	i) Cyclin D ii) Cyclin E iii) CDK4

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Carcinoma due to inherited mutation of p53 protooncogene -

a) Li fraumeni syndrome
b) Familial adenomatous polyposis
c) Retinoblastoma
d) Osteosarcoma

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A

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Hereditary retinoblastomas develop the following chromosomal deletion [Rb Gene location]-

a) 13q14
b) 13p14
c) 14p13
d) 14p13

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A

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A child is born with a single functional copy of a tumor suppressor gene. At the age of 5 years, the remaining normal allele is lost through mutation. As a result, the ability to control the transition from G1 to the S phase of the cell cycle is lost. Which of the following neoplasms is most likely to arise by means of this mechanism -

a) Retinoblastoma
b) Breast carcinoma
c) Adenocarcinoma of colon
d) Cerebral astrocytoma

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A

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Loss of hetrozygosity associated with -

a) Acute myeloid leukemia
b) ALL
c) Retinoblastoma
d) Promyelocitic leukemia

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c

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The most common secondary malignancy in a patient having retinoblastoma is:

(a) Osteosarcoma
(b) Renal cell carcinoma
(c) Pineoblastoma
(d) Osteoblastoma

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A

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Which is not a tumor suppressor gene?

(a) WT-1

(b) Rb

(c) p53

(d) ras

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D

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The inheritance pattern of familial Retinoblastoma is:

(a) Autosomal recessive

(b) Autosomal dominant

(c) X-linked dominant

(d) X-linked recessive

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B

- Retinoblastoma is a prime example of a tumor which is associated with loss of heterozygosity.
- • Rb gene is a tumor suppressor gene located on chromosome **13 q14Q.**
- • Retinoblastoma develops when both the normal alleles of the Rb gene are inactivated or altered.
- • Familial retinoblastoma is associated with **autosomal dominant inheritance** whereas the Rb gene is having **autosomal recessive inheritance.**

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Which of the following is known as the "guardian of the genome"?

(a) p53
(b) Mdm2
(c) p14
(d) ATM

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A

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The following statements are true about Tumor Suppressor Gene p53, except:

(a) It regulates certain genes involved in cell cycle regulation

(b) Its increased levels can induce apoptosis

(c) Its activity in the cells decreases following UV irradiation and stimulates cell cycle

(d) Mutations of the p53 gene are most common genetic alteration seen in human cancer

c

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Tumor suppressor genes are all, except

(a) APC
(b) p53
(c) Rb
(d) C-myc

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D

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Knudson two hit hypothesis is seen with

- (a) Melanoma
- (b) Retinoblastoma
- (c) Ulcerative colitis
- (d) Crohn disease

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Thank you for being awake

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28 Nov - Drugs for Asthma
01 Dec - Oral Hypoglycaemic Agents and Insulin
03 Dec - CNS - Sedatives and hypnotics, Alcohol
05 Dec - CNS - Anti Parkinson's drug
08 Dec - Drugs affecting RAS
10 Dec - Anti-angina and Heart failure drugs
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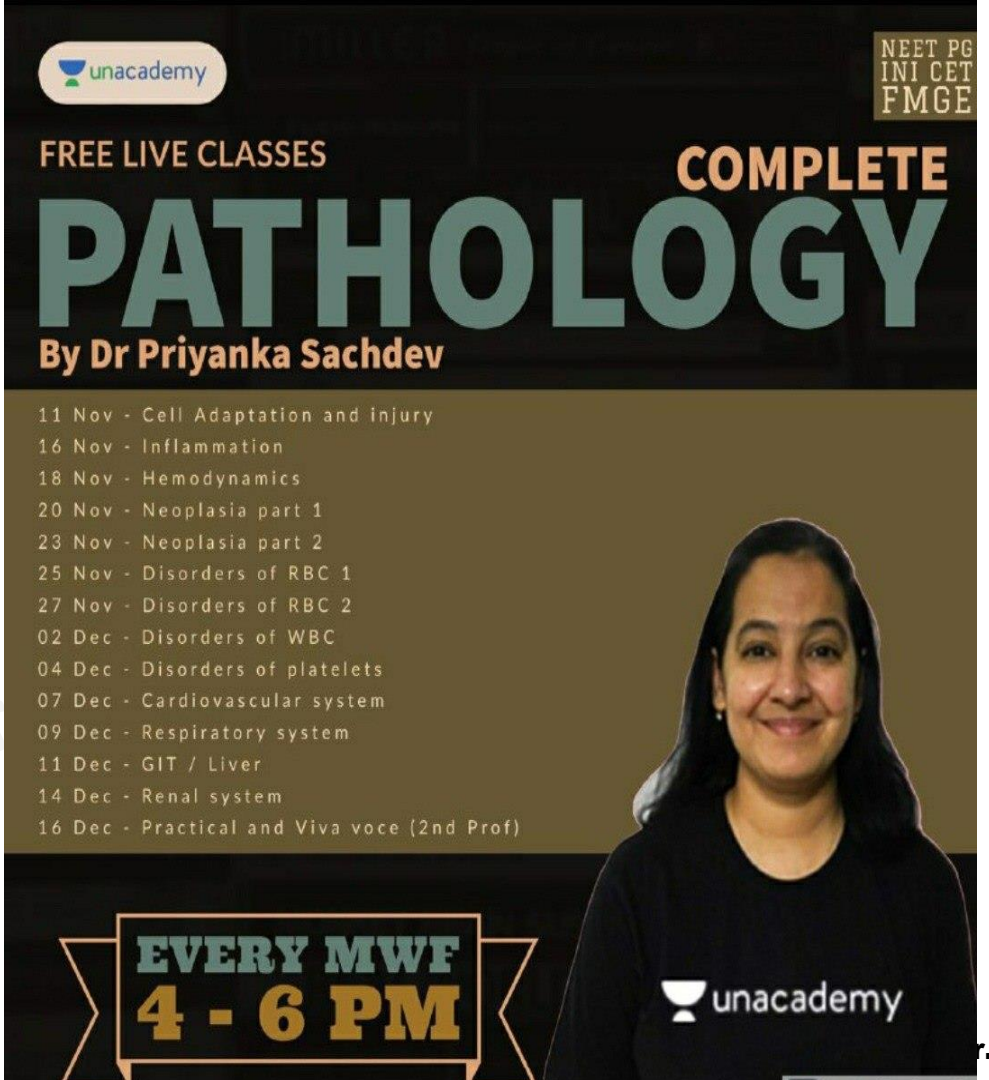
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27 Nov - Disorders of RBC 2
02 Dec - Disorders of WBC
04 Dec - Disorders of platelets
07 Dec - Cardiovascular system
09 Dec - Respiratory system
11 Dec - GIT / Liver
14 Dec - Renal system
16 Dec - Practical and Viva voce (2nd Prof)
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